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This project started over two years ago when the AIDS Community Research Initiative of America gave a presentation to the American Academy of HIV Medicine staff on their comprehensive study Research on Older Adults with HIV (ROAH) of 1000 New York City older adults living with HIV. It was the first time we learned that the HIV epidemic was now aging as a function of the enormous improvements in HIV treatment over the past 30 years. Effective treatment now extends the lives of those with HIV so that by mid-decade half of all those living with HIV in the U.S. will be age 50 and older. These older adults, well before they can be called seniors, are developing many illnesses more typically associated with advanced age. The Treatment of these co-morbidities, as well as HIV infection, presents new challenges for HIV practitioners—but without any real clinical guidance.

The American Academy of HIV Medicine led the effort on developing a clinical guidance for practitioners who were already treating such patients with the American Geriatrics Society (AGS) signing on as a supporting organization.

Dr. Wayne McCormick, a member of the AGS’ board of directors, and Dr. Jon Appelbaum, from the American Academy of HIV Medicine board of directors, were selected as the Principal Investigators. Both Drs. Appelbaum and McCormick are practicing geriatricians as well as HIV specialists. Over the intervening eighteen months, a fourteen-member expert panel was convened, contributed chapters from their field of experience, and authored this comprehensive report.

In addition to our thanks to Drs. Appelbaum and McCormick and all the panel members, we want to acknowledge the enormous efforts of Ken South of the American Academy of HIV Medicine, Marianna Drootin of the American Geriatrics Society and Stephen Karpiak, PhD and Dr. Richard Havlik of the AIDS Community Research Initiative of America. Similarly we wish to acknowledge Tibotec (now Janssen Pharmaceuticals), Strativa Pharmaceuticals, and the Campbell Foundation without whose support, this undertaking would not have been possible.

We feel confident this report will contribute to the quality of care delivered to older patients living with HIV disease. Further, we acknowledge that there remain substantial gaps in our knowledge base. But we will keep this a living/growing process that will be continually updated using an interactive web site that will allow practitioners and researchers to report on their clinical experience with older HIV patients.

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INTRODUCTION

By mid-decade the CDC predicts that nearly half of the expected 1.5 million in the USA living with HIV (Human immunodeficiency virus infection) will be age 50 and older. This aging of the epidemic is largely the result of effective ARV (Antiretroviral) treatments which have prolonged the life span of those with HIV disease. During the past decade, several organizations have convened groups to assess the state of knowledge and science at the nexus of HIV and aging, including a White House Office of National AIDS Policy Special Meeting on HIV and Aging in October 2010. The NIH has recognized the emerging issue by establishing intra- and extramural workgroups in early 2011. As the lines of communication have grown between HIV care providers and geriatricians, common themes have emerged involving the health management of older persons with HIV infection. Members of the Academy of HIV Medicine (AAHIVM) and the American Geriatrics Society (AGS) with the AIDS Community Research Initiative of America (ACRIA) have collaborated for the past two years to address the clinical management of older persons with HIV/AIDS.

The Complications of Success

Among those with HIV infection receiving HAART, the proportion achieving viral suppression is growing, aging, and experiencing a widening spectrum of “non AIDS” diseases (Deeks & Phillips 2009). Concurrently, AIDS defining conditions are less common (Monforte et al. 2005) and correlate with CD4 count and mortality (Mocroft et al. 2009). Further, while life expectancy among those on HAART has increased dramatically, it is not “normal” (Losina et al. 2009). There is increasing evidence that HIV infected individuals on HAART experience an array of “non AIDS” conditions associated with HIV infection, HIV treatment, and/or behaviors, conditions, and demographics that typify those with HIV (Justice 2010; Deeks & Phillips 2009). The evidence describes an older adult population living with HIV, most of whom are between the ages of 50 and 65 years, who are experiencing high rates of comorbid illnesses (Havlik et al. 2011; Deeks & Phillips 2009). The interaction of aging and HIV may be frequently manifested by elevated risk for comorbidities which include liver disease (could be hepatitis-related), cardiovascular disease, kidney impairment, non-AIDS cancers, osteoporosis, neurocognitive decline, and "frailty" which is characterized by weight loss, weakness, and increased risk of disability and death. This multi-morbidity contributes to overlapping injury to multiple organ systems (Justice 2010; Deeks & Phillips 2009). The result is the transformation of HIV infection into a complex chronic disease associated with multi-morbidity requiring the attention and expertise of multiple health care domains and their providers (Sevick et al. 2007). We do not know at this time what the underlying mechanism of this change is. The comorbid conditions occurring in those with HIV and on HAART are often defined as “non-AIDS”. However they are associated with HIV infection (HIV associated non-AIDS or HANA), HIV treatment, and/or behaviors, conditions, and demographics more common among those with HIV infection (Justice 2010; Deeks & Phillips 2009).
The “non-AIDS” conditions experienced by those with HIV infection may be strongly influenced by HIV, HIV treatment, and behaviors and conditions more common among those with HIV. Thus, these conditions may behave somewhat differently among those with HIV infection compared to uninfected individuals.

These HANA conditions are common in the general aging population who are without HIV disease. But since they occur in association with HIV, one can conclude that HIV infection, its treatments and the long-term results may be significant factors. Multiple mechanisms have been suggested, including microbial translocation, chronic inflammation, oxidative stress, and immune senescence (Purohit et al. 2009; Butt et al. 2004; Butt et al. 2009; Crothers et al. 2011). More studies are exploring the risk factors among those with HIV infection for these “non-AIDS” conditions. In addition to expected associations with known risk factors there is an increased risk for many non-AIDS conditions among HIV infected individuals when compared to uninfected subjects. As a group these studies demonstrate that traditional risk factors together with the risks variables of HIV, HIV treatment, and in some cases, HCV co-infection (Butt et al. 2011; Butt et al. 2009; Butt et al. 2010) combine to establish the patient’s overall risk for morbidity and reduced life-span.

*Assessing Frailty and Functional Capacity*

Overlapping geriatric syndromes such as “frailty”, “disability”, “multimorbidity”, and “polypharmacy” require adaptation for those aging with HIV infection to account for the ongoing role of HIV infection and its treatment in modifying the aging process. Several complementary approaches to the measurement of frailty have evolved within the geriatric literature and these have been variably applied among those aging with HIV. The approach most often employed in the HIV literature, uses a triad of wasting, slowing, and weakness and is characterized by the frailty phenotype and the frailty related phenotype (Desquilbet et al, 2011; Fried et al., 2001). Another approach focuses on cumulative deficits across multiple physiologic systems (Clegg et al., 2013), but it requires 30 separate measures and has been deemed less feasible for routine care. Rockwood et al have proposed a reduction in the number of measures from 30 to 10. Some have suggested that a single measure of function, such as grip strength or the six minute walk test, might serve.

Whether you prefer a phenotype, accumulated deficits, or a test of strength or speed, the clinical variables most likely to indicate increased vulnerability among those aging with HIV infection are likely different than in the overall aging population. Immunodeficiency and persistent viral burden are important. Similarly, anemia, hepatitis C coinfection, renal and liver disease are also more common and likely, important. As mentioned above, gross functional limitations are rare. Wasting is increasingly rare after ART initiation. In contrast, obesity is increasing (especially after ART) but may or may not have the same implications as obesity among uninfected individuals.

The Veterans Aging Cohort Study Index (VACS Index) combines routine clinical measures of immunodeficiency, viral load, and organ system compromise (CD4 count, HIV-1 RNA, hemoglobin, creatinine, aspartate and alanine transferase, platelets, and HCV status)to estimate risk of morbidity and mortality (Justice at al. 2009).
It has demonstrated generalizable predictive accuracy for all cause (Justice at al. 2013) and cause specific mortality (Tate et al., 2013) and for hospitalization (Akgun et al., 2013), medical intensive care unit admissions (Akgun et al., 2013), and fragility fractures (Womack et al., 2013). It is cross-sectionally associated with markers of chronic inflammation (Justice at al., 2012), cognitive performance (Franklin et al., 2013), and functional performance (Erlandson et al., 2013). Its discriminatory accuracy is consistent across important clinical subgroups. The VACS Index appears to be a reasonable measure of frailty that is clinically feasible. Whether it can be improved by the addition of a measure of functional performance, sarcopenia, cognitive performance, multimorbidity, or additional measures of physiologic compromise remains to be determined.

Like those aging without HIV infection, vulnerability to injury resulting from depleted physiologic reserve is caused by multiple overlapping and interacting mechanisms including multiple comorbid conditions (multimorbidity) and polypharmacy. Compared to those without HIV infection, individuals aging with HIV infection are at increased risk of multimorbidity due to hepatitis C co-infection and HIV Associated Non AIDS (HANA) conditions which are increased after adjusting for established risk factors. Those with HIV experience multimorbidity (Goulet et al., 2007) and polypharmacy (5 or more medications) (Edelman et al., 2013a; Edelman et al., 2013b) earlier than demographically matched uninfected comparators.

Recent data suggests that low social support translates into increased hospitalization mortality in this population (Greysen et al., 2013). Almost 70% live alone, estranged from their families and friends as a function of AIDS associated stigma (Brennan et al. 2011; Emlet 2006; Shippy & Karpiak 2005; Karpiak 2006; Brennan et al. 2009). As a result they have fragile social networks that are not a resource for the informal caregiving they will need in order to age successfully (Shippy & Karpiak 2005; Brennan-Ing et al., 2014). Ostracized and rejected, many isolate themselves with a self-protective withdrawal where they hide their HIV status. Others choose to be isolated because they have lost their friends and extended families to HIV/AIDS. Without functional social supports from which care and assistance can be obtained this population will seek more formal supports in a period of reduced economic resources (Storholm, E. D., et al. 2013; Longmire-Avital, et al. (2012). Without such support they will be relegated at early ages to costly home health care services and long-term care facilities (Brennan-Ing et al., 2014). Choosing treatment strategies for an older adult with HIV must consider their often poor support networks (Emlet 2006; Vance et al. 2011; Vance et al. 2010; Shippy & Karpiak 2005; Karpiak 2006).

In addition the co-occurrence of mental health issues and substance use is a common characteristic for this population. But middle aged and older adults with HIV are not typical of the general aging population (Karpiak 2006; Brennan et al. 2009). They evidence high rates of depression and suicidal ideation that contribute to reduced health outcomes (Havlik et al. 2011) (Oursler et al. 2006). As they age, many use alcohol, tobacco, and/or illicit drugs, further compromising their health (Grov et al. 2010; Golub et al. 2010; Siconolfi, D. E., et al. (2013). This is an older, but not senior, population that has difficulties with day-to-day tasks, including housekeeping, transportation, meal preparation, employment, finances, and
entitlements (Oursler et al. 2011, Oursler et al. 2006; Oursler et al. 2009; Brennan-Ing et al., 2014).

Lessons from Geriatrics: Tailoring Care for Syndromes

Besides describing the diverse etiologies that drive frailty and disability among those aging with complex chronic (Walston et al. 2006; Tinetti et al. 2004) the geriatric literature offers two additional lessons for the management of those aging with HIV. First, geriatricians warn against the blind application of screening and treatment guidelines developed for application in a primary care population free of major co-morbidity to those with complex chronic disease and multi morbidity (Tinetti et al. 2004). Multi-morbidity is the norm among those aging with HIV. In one analysis, 65% of HIV infected individuals between 50-59 years of age had at least one co-morbid diagnosis and 7% had a medical co-morbidity, a substance use disorder and a psychiatric diagnosis (Goulet et al. 2007). We must prioritize and tailor care for those aging with HIV based upon a careful assessment of their risk of morbidity and mortality, an identification of risks which are modifiable, and the goals of the individual patient (Bradley et al. 1999; Tinetti et al. 2008) and target interventions based upon this assessment. Second, geriatricians emphasize syndromes and severity of disease over particular diagnoses (Tinetti 2004; Bradley et al. 1999; Karlamangla et al. 2007; Lachs et al. 1990). Thus it may be more important to identify organ systems at risk rather than labeling all diagnoses present in an individual. Some diagnoses (e.g. vitamin D deficiency) may never become symptomatic, whereas organ system failure is always associated with substantial morbidity and mortality.

Although antiretroviral therapy successfully suppresses viral replication, numerous studies have demonstrated decreased immune reconstitution with increasing age. A recent study showed that older patients were more likely to achieve virologic suppression than younger patients, but had smaller increases in their CD4 count at 2 years after HAART initiation. In addition, there was no difference in viral suppression or CD4 increase by ART regimen type boosted protease inhibitor (PI) vs. non-nucleoside reverse transcriptase inhibitor (NNRTI) between age groups (Althoff et al. 2010).

There are some data to suggest that there is premature aging of the immune system in the setting of HIV infection. Several studies have shown increased levels of immune activation despite sufficient viral suppression. For example, the SMART study demonstrated increased levels of numerous immune markers including of interleukin 6 (IL-6), D-dimer, and high sensitivity C reactive protein (CRP) compared to HIV-uninfected patients (Kuller et al. 2008). But it must be noted that these studies used population based uninfected comparators that were not behaviorally or demographically similar to those with HIV infection. Importantly, rates of HCV co infection, smoking, and alcohol consumption—all of which may influence these markers, likely differed among these groups.

Older patients experience immunosenescence as they age. This is manifested not only by increased immune markers but also by reduced level of naïve CD8+ cells, increased levels of terminally differentiated effector CD8+ cells, increased T cell activation, and reduced T cell proliferation. This immunologic picture can be exacerbated in the setting of chronic viral infection. It is likely that residual viral
replication and the loss of cells that regulate immune modulation may further impair the immune system. However, it is unknown currently how these parameters change in the setting of co-infection with multiple viruses such as HIV, hepatitis B and/or C and CMV.

Strategies of care that are likely to prevent and reverse functional compromise and frailty whenever possible will include early HAART, but also include behavioral interventions to improve adherence, motivate decreased alcohol consumption, encourage smoking cessation, avoid obesity, and support exercise. Careful consideration of potential treatment toxicity from HIV and non-HIV medications is also likely to be important. Because this list of interventions is long, prioritization will become increasingly necessary (Boyd et al. 2005; Lee et al. 2006; Boyd et al. 2007). The Veterans Aging Cohort Study Risk Index (VACS Index) offers a more comprehensive approach to estimating the burden of disease experienced by a patient with HIV infection and identifying organ systems at risk. It uses laboratory tests routinely obtained in the course of HIV care to predict risk of adverse outcomes incorporating age, CD4 count, HIV-1 RNA, hemoglobin, aspartate and alanine transaminase, platelets, creatinine and hepatitis C virus (HCV) (Brown et al. 2010) (Justice et al. 2010). The Veterans Aging Cohort Study Risk Index (VACS Index) offers a more comprehensive approach to estimating the burden of disease experienced by a patient with HIV infection and identifying organ systems at risk. It uses laboratory tests routinely obtained in the course of HIV care to predict risk of adverse outcomes incorporating age, CD4 count, HIV-1 RNA, hemoglobin, aspartate and alanine transaminase, platelets, creatinine and hepatitis C virus (HCV) (Brown et al. 2010) (Justice et al. 2010). It discriminates mortality among those initiating HAART better than an index restricted to CD4 count, HIV-1 RNA, and AIDS defining illnesses (Justice et al. 2010). While initially developed and validated among veterans in care, the index has been shown to be equally predictive of mortality among veteran and nonveteran subjects initiating salvage HAART (Brown et al. 2010) and among those on ART participating in the NA-ACCORD cross cohort collaboration (Justice et al. 2011). The index also differentiates risk of admission to a Medical Intensive Care Unit (Akgun et al. 2010).

The use of a more comprehensive risk index could encourage us to consider more broadly the mechanisms that may contribute to total burden of disease among those aging with HIV infection. These include inevitable tradeoffs in chronic disease management between screening for and aggressively treating every co-morbid condition and the risk of injury from poly-pharmacy, drug-drug interactions, and cumulative toxicity (Gebo & Justice 2009).

HIV infection and its consequences continue to play a role in health outcomes. This role interacts with cumulative effects of health behaviors, aging related co-morbidity, and medication toxicity to drive morbidity and mortality. Taken together, these developments underscore the need to go beyond CD4 count, viral load and AIDS defining conditions to develop a more comprehensive risk index of morbidity and mortality to guide clinical care and research.

*Multi-Morbidity*

Multi-morbidity is a syndrome familiar to geriatricians and often observed among older HIV patients; it is more than simple co-morbidity. Multi-morbidity is conceptualized as several serious health conditions that cannot be cured to any great extent, occurring in an older person and engendering functional and/or cognitive debility. When considering treatment options in persons with multi-morbidity, the sum is greater than the parts. Aging plus debilitating conditions have the propensity to synergize to make morbidity and mortality worse than might otherwise seem apparent. In one study, the survival of older individuals with multi-morbidity was similar to populations of persons with
metastatic colon cancer (Gross et al. 2006). The Panel sought to incorporate geriatric syndromic thinking into the considerations of clinical guidance taking into account multi-morbidity, frailty, and aging as distinct from chronological age. These considerations pervade each recommendation.

Multi-morbidity is increasingly becoming the norm rather than the exception among people with HIV infection. (Kim et al., 2012; Haase et al. 2011; Deeks et al. 2013). Patients with HIV are surviving long enough to experience HIV as a chronic disease, as well as a broad spectrum of co-morbidities. Non-AIDS-defining conditions including chronic kidney disease, metabolic and cardiovascular disease, and malignancies have been observed as increasing in incidence in recent years (Bonnet et al. 2004; d’Arminio Monforte et al. 2005; Gebo et al. 2005; Salmon-Ceron et al. 2005; Palella et al. 2006; Baker et al. 2007; Friis-Møller et al. 2010; Braithwaite et al. 2008; Braithwaite et al. 2005; Haase et al 2011). Globally, there is increasing recognition of the growing incidence of multimorbidity in the industrialized and developing world (Phaswana-Mafuya et al. 2013; Deeks et al 2013). Multimorbidity associated with HIV disease could affect healthy aging and overwhelm some healthcare systems, particularly those in countries that have not yet fully addressed the chronic disease epidemic in their health care systems. (Deeks et al 2013). Furthermore, evidence is emerging that multimorbidity contributes to health disparities between groups (Vila-Rodriguez 2013).

The report contains many specific recommended treatment strategies for pairs of conditions, i.e., HIV and kidney disease. Some of these focus on HIV and the prevention of another disease, and some focus on the management of a patient with HIV and another condition. Cumulatively, this would result in a litany of recommendations for treatment of HIV, for the treatment of other illnesses, and preventive treatments. But it is known that if one applies disease-specific guidelines to a patient with multiple illnesses (e.g. hypertension, diabetes, osteoporosis, COPD and osteoarthritis, and HIV) the resultant treatment regimen is complex, involves a large number of disease specific medications and presents a demanding dosing pattern (Boyd et al. 2005). This particular constellation of diseases would not be uncommon in an older person with HIV/AIDS. The challenge is daunting when adding the complex management issues of HIV to an even-more complicated multimorbidity treatment regimen with the added implications of adherence as well as drug-drug, drug-disease and disease-drug interactions (Braithwaite et al. 2005). An increasing number of comorbid conditions in people living with HIV is directly linked to an increase in the number of total medications (Haase et al. 2011). Approaches to polypharmacy in people living with HIV merit further investigation, and must factor in the unique aspects of multimorbidity in HIV (Edelman et al 2013). If mental illness is present, cognitive impairment, substance use, or limited health literacy, an older adult’s ability to adhere to such complex treatment regimens would be low (Stone et al. 2001). Most studies in HIV have focused on adherence to antiretroviral treatment (ART) but how treatment of other conditions affects adherence to HAART, and adherence to the overall treatment regimen is not known. Research suggests that variation in adherence patterns to ART and other treatments varies depending on symptom attribution, medication concerns, and coping strategies (Batchelder et al 2013; Wendorf et al. 2013).
Methodology

An Expert Panel comprised of members from AAHIVM and AGS, staff, and two Co-Principal Investigators guided the effort. Two researchers in HIV and aging from ACRIA provided additional expertise and support. The effort began in late 2009 to formulate guidance for clinicians caring for older persons with HIV infection. The Panel agreed that the term “older” in the context of persons with HIV infection, pertained to age 50 or greater. This is both a matter of convention (as established in the sections that follow), and epidemiology, since a majority of people with HIV infection will be over 50 before the end of this decade, many with a substantial burden of illness (Justice 2010). Half of the 14 member Expert Panel had significant clinical and research experience in geriatrics. The other half were acknowledged leaders in HIV care and research. Several panel members were experienced in both HIV treatment and geriatrics. Panel members received modest honoraria for expenses and absence from employment and were blinded to sources of the study funding.

The Panel developed a Consensus Strategies Working Document, using the Modified Delphi technique (see below). This technique, commonly employed to reach consensus in groups, involved serial periods of input from Panel members, followed by feedback from conference and individual calls every 2-4 weeks. The Consensus Strategies Working Document, evolved with several iterations of input / feedback to develop a list of areas most in need of clinical guidance. The Co-PIs engaged Panel members in phone and email discussions/queries when needed. Panel then met face-to-face to discuss recommended treatment strategies and the evidence for them, and also to indicate their collective confidence in each suggestion. To inform consensus, each panel member rated each recommended management treatment strategy on their level of confidence and prioritization (see Appendix). After confidential compilation, the data were given to the panel members. Several treatment strategies received mixed ratings. Only those receiving high levels of confidence and priority with high levels of consensus were retained. Any redundancies in text were edited and combined. The remaining recommendations were again circulated to the panel members who again rated each recommendation. The resulting data was assessed by the Co-PIs to assure there was consensus and all edits and changes provided by the panel were integrated into the working document. The resulting document was submitted to 6 other experts in HIV and aging for review. They were instructed to review the entire document for clinical sensibility and reasonableness of the recommended treatment strategies. The reviewers were identified by Panel members, but had not participated in the consensus process. These management suggestions are presented with available evidence. Ideally supporting evidence would be peer-reviewed data derived from studies of HIV infected subjects over 50 years of age. The Panel recognized the lack of such clinical data regarding this population and referenced other clinical data which support the recommended treatment strategies. The Panel recognizes that this is a rapidly evolving field, and new evidence will no doubt amass that will either bolster or refute the suggested treatment strategies presented in this manuscript. Nevertheless, the Panel felt that some guidance was better than none, to help practitioners treat the coming wave of persons with HIV/AIDS entering
their sixth and seventh decades of life. Some of these suggested treatment strategies are not different than current treatment guidelines for younger patients with HIV/AIDS, or for uninfected older patients. We hope that practicing clinicians will use the information as a foundation for caring for older individuals with HIV/AIDS, and that recommended treatment strategies will be modified in the future by the results of high-quality clinical investigations in this population. The recommended treatment strategies herein are not guidelines – they represent consensus opinions of the group.

**Modified Delphi Technique**

Delphi techniques provide a structured process for eliciting and correlating informed opinions and information from a panel of experts on a given topic. Data collection occurs through an iterative process that incorporates the use of questionnaires that are accompanied by group led feedback processes (email, phone conference calls, individual phone and face-to-face discussions). The process is focused on having the panelists arrive at consensus on a subject, yet the process can also identify varying opinions even when consensus is not achieved.

Delphi techniques have been widely used to develop educational guidelines, establish practice competencies, and generate research agendas in aging. These include Educational Program Standards in Gerontology, established learning objectives to prepare social workers for case management with frail elders; developed geriatric fellowships and residency training requirements; assessed geriatric education needs of entry-level physical therapists; and determined information needs of older (Gilford & Frank 2006) adults. Delphi panels have identified key social, environmental, and economic aspects of geriatric assessment, as well as the primary needs of rural elders; taxonomies of elder abuse; typologies of practitioner problems in health services to elders. Delphi techniques underlie proposed research and policy priorities in specific areas of gerontology including research topics to meet health needs of aging veterans, guidelines to protect human subjects in long-term-care research as well as a series of prognostications about the future of long-term care in the US.

Each expert panel members completed a disclosure form at the beginning of the guideline process that was shared with the entire expert panel at the start of its expert panel meetings. Conflicts of interest in this report have been resolved by having the guideline independently peer reviewed and then edited by the Expert Panel Chairs.

The report was also reviewed by key leadership at the American Academy of HIV Medicine, the American Geriatrics Society, and the AIDS Community Research Initiative of America

Expert panel members who disclosed affiliations or financial interests with commercial interests involved with the products or services referred to in the guideline are listed under the disclosures section of this article.

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Justice, A, C. 2011. A prognostic index for those aging with HIV: Extension of the VACS index to those on cART


We recommend routine, opt-out screening for HIV in all adults, including those over the age of 65. As described below, HIV screening based on identification of risk factors alone is not effective, especially since older adults may be more likely than the general population to have unrecognized risks, and are therefore more likely to present late in the course of infection with HIV/AIDS. Since early initiation of antiretroviral therapy is critical to successful treatment, and routine screening is more effective than risk-based screening in identifying HIV earlier in older adults, we recommend that all adults regardless of age should be screened for HIV.

The number of older adults with HIV/AIDS is increasing, partly because people with HIV/AIDS are living longer. In 2010, 19% (217,300) of those with HIV in the U.S. were over the age of 55, and it is estimated that by 2015 this will increase to 50% (CDC 2013, CDC 2011). There has also been a continued lack of attention to the rate of new infections in older adults. In 2011, 47% of new infections were in those 50-55 years old, and in 2010, 5% of new infections were in those over 55 years old (CDC 2013). One in 6 of all new HIV infections in the US occur in the older adult (CDC 2011), and in 2011 older adults accounted for 24% of AIDS diagnoses (CDC 2013).

Detecting HIV in older adults is not only important because of the increasing incidence and prevalence, but also because older adults are more likely to present late, with greater associated mortality (Chadborn et al. 2006). A UK study found that 48% of older adults were late presenters vs. 33% of younger adults (Smith et al. 2010). Older adults in this study were 14 times more likely to die within a year of diagnosis compared with older adults who were not diagnosed late. Reasons for late diagnosis include lack of awareness by both patients and providers.

Screening for HIV/AIDS requires awareness of risk factors, which may be different in older adults. In contrast to younger adults, the main risk factor in older adults is heterosexual intercourse, though the route of HIV infection is often unknown (Grabar et al. 2006; Martin et al. 2008; Sherr et al. 2009). There are however differences based on gender, with 60% of men over 50 years old contracting HIV by male-male sexual contact, 23% heterosexual contact, and 14% injection drug use, as compared to women with 82% by heterosexual contact and 16% by injection drug use (CDC 2013). Older women may be at increased risk of HIV due to age-related vaginal thinning and dryness, and also because older women starting a new sexual relationship after many years of being in a monogamous relationship may find it...
difficult to initiate discussions about risks and the use of condoms (CDC 2013). Additionally, increasing prevalence of erectile dysfunction as men age may make condom use even more challenging, while the availability of medication to treat erectile dysfunction may also allow for increased sexual activity in older men (CDC 2013).

Minority races/ethnicities may also have increased risk factors (Zingmond et al. 2001, Linley 2012). The rate of new HIV diagnoses in older Blacks and Hispanics/Latinos was 12.6 and 5.0 times higher than Whites (Linley et al. 2012). Older adults who are lesbian, gay, bisexual or transgender (LGBT) are an additional group at increased risk, especially men who have sex with men, who account for just about half of all new HIV infections (CDC 2013). Older LGBT adults are often invisible to the health care profession for multiple reasons, which can further impair effective communication and reduction of risk (Grossman 1995; Simone & Appelbaum, 2011).

**Barriers to effective prevention and detection include:**

1. Lack of knowledge about HIV/AIDS by older adults/reluctance to discuss sexuality: Older women have poor knowledge about HIV risk factors (Henderson et al. 2004). Older adults are also often ignored or forgotten in typical prevention campaigns that generally target youth (Pratt et al. 2010). Older patients also report receiving little information about sexual health, HIV, and other STIs from their physicians, despite still being sexually active (Lindau et al. 2007; Stall & Catania 1994). Many older people do not consider themselves at risk for contracting HIV and therefore do not get tested. A 2009 survey of over 12,000 older adults found that only 25% had ever been tested, and of those tested, 70% had been more than 5 years ago (Adekeye et al. 2012). Respondents identified very low perceived risk of HIV infection (98% reported risk as low or none), and lower perception of risk was associated with decreased likelihood of being tested. Older adults are much less likely to use condoms than younger adults. For instance, only 20% of men and 24% of women reported condom use during their last sexual encounter, and yet the majority of men (64.4%) and women (68.9%) reported that they had not received an STI test within the past year (Schick et al. 2010). A systematic review of HIV prevention programs that target older adults suggests three models of education: group education programs delivered by social workers or other health professionals, peer education models, and one-on-one early intervention models including HIV/AIDS testing (Milaszewski et al. 2013). Increasing attention has been paid to the critical need for more effective prevention programs for older adults, as was discussed at a White House summit on HIV and aging in 2010. Various resources and campaigns now exist (Brooks et al. 2012).

2. Underestimation of risk by healthcare providers/ageism: Healthcare providers may not consider discussing HIV/AIDS with older patients, and may also lack the correct knowledge about risk factors in older patients (Skiest & Keiser 1997). They may incorrectly assume that older patients are not sexually active or do not use drugs, or may be uncomfortable raising these issues with older patients (CDC 2013, Brooks 2012). Providers are also much less likely to document the sexual history of older adults (Loeb et al. 2011). However, older adults remain sexually active: 53% of those 65-75 years old, and 26% of those 75-85 years old, report sexual activity (Lindau et al. 2007). In addition, older adults with HIV also remain sexually active (27%), with only 68% reporting consistent condom use (Onen et al. 2010). A national survey of providers found that they had difficulty ranking the four most common
risk factors for HIV infection in older adults, and only 6% was able to correctly rank all four (Hughes 2012).

Misdiagnosis/delay: Making the diagnosis of HIV/AIDS in older adults can be challenging because the symptoms can mimic normal aging or other medical conditions common in the elderly, such as fatigue, weight loss and mental confusion (Lekas et al. 2005). A retrospective analysis of HIV positive women found missed opportunities for diagnosis in their older cohort (>44 years old), who were also more likely to be late-testers (diagnosed with AIDS <12 months of diagnosis of HIV), and they were more likely to have no identifiable risk factor for HIV transmission (Duffus et al. 2012).

Stigma: HIV-infected older adults with HIV may be more likely to experience greater stigma from their peers due to the association of HIV with homosexuality and substance abuse, leading them to hide their diagnosis or risk factors from providers or family (CDC 2013). Unfortunately, older patients have little interest in HIV testing, even in the presence of risk factors (Akers et al., 2007; Lekas et al. 2005; Mack & Bland, 1999).

Communication between health care providers and patients is critical for HIV prevention and detection, and providers must address the barriers to effective screening and discussion. For example, providers need to discuss safer sex methods with their older patients. Providers must use medical histories that include questions regarding older adults’ sexual behavior, sexual orientation, and substance use. Providers play an important role in testing since provider endorsement is associated with higher rates of screening (Craig et al. 2012). Not only should providers have a lower threshold to screen for and consider the diagnosis of HIV in older patients, but they must also engage patients of all ages in discussions about sexual health and risk prevention. (see Sexual Health section). Removing unnecessary barriers to testing, such as the need for written consent, also improves screening rates (Nayak et al. 2012).

The Centers for Disease Control and Prevention (CDC) recommends voluntary, routine opt-out HIV screening for all adults age 13-64, regardless of risk factors (Branson et al. 2006). Those with known risk factors should have repeat HIV screening at least annually. These guidelines discourage screening based solely on risk factors, because targeted testing in the general population on the basis of risk behaviors alone fails to identify a substantial number of persons who are HIV infected (Branson et al. 2006). In 2013, the U.S. Preventive Services Task Force updated their screening recommendations, and similar to the CDC, recommend routine screening for all adolescents and adults age 15-65 (grade A recommendation) (Moyer et al. 2013). These recommendations unfortunately provide a cut-off at 65 years old, at which point routine screening is no longer recommended, despite the fact that older adults and providers are unable to correctly identify risk factors for HIV infection (Henderson et al. 2004; Skiest & Keiser, 1997). Analyses of HIV screening in older adults show that one-time routine screening of adults up to the age of 75 may also be cost-effective (Sanders et al. 2005).

Given that the cost and risk of physical harm from an HIV test is much less than other established screening tests (e.g. colonoscopy), and since the potential benefits of earlier detection are great, we recommend routine screening of all older adults. Routine screening is more effective than risk-based screening, perhaps even more so in older adults, where providers and patients are less likely to identify risks for HIV infection. In addition to the public health benefit of reduction in HIV transmission in older patients, routine screening may also improve
individual outcomes as a result of earlier treatment (the treatment of HIV/AIDS in older adults is discussed separately in this document). Unlike most screening recommendations in the elderly which should account for the individual’s functional status, comorbidities, and predicted life expectancy, we recommend routine testing of all older patients, regardless of age or individual factors, since effective and acceptable treatment options exist, and routine detection would reduce further transmission of HIV in the older population.

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Multiple cohort studies involving untreated HIV-infected persons have established that older persons have a more rapid progression to AIDS and shortened survival when compared with younger persons (Phillips et al. 2008; Balslev et al. 1997; Rezza 1998; Egger et al. 2002). For HIV-infected persons older than 50, sparse data exist from randomized, controlled antiretroviral therapy clinical trials, as most randomized therapy trials have excluded persons older than 50 or 60. A retrospective analysis of 253 patients 50 years of age or older found antiretroviral therapy substantially improved survival rates (Perez & Moore 2003). Several large retrospective studies have clearly shown delayed and diminished CD4 cell recovery after starting antiretroviral therapy in older HIV-infected patients when compared with younger age groups (Khanna et al. 2008; Silverberg et al. 2007; Althoff et al. 2010; Cohere 2008).

Studies have shown conflicting results with respect to virologic responses in older versus younger (Silverberg et al. 2007; Paredes et al. 2000; Manfredi et al. 2003; Lampe et al. 2006), with the most comprehensive study showing no significant difference in virologic responses based in older versus younger adults (Althoff et al. 2010).

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

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

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*When to Initiate Antiretroviral Therapy in HIV and Aging*

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

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

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The two major antiretroviral therapy guidelines that most influence clinical practice in the United States—the Department of Health and Human Services (DHHS) Panel guidelines (OARAC DHHS - 2011) and the International AIDS Society USA (IAS-USA) Panel guidelines (Thompson et al. 2010) have limited guidance regarding antiretroviral therapy for persons 50 and older. The January 2011 guidelines state initiating antiretroviral therapy at an older age consistently results in poorer CD4 recovery than seen in younger patients, thus inferring a need for initiation of antiretroviral therapy at higher CD4 cell counts in this patient population (OARAC DHHS - 2011). The July 2010 IAS-USA Guidelines recommend initiating antiretroviral therapy regardless of CD4 count in persons older than 60, but do not address this issue in persons 50-60 years of age (Thompson et al. 2010). Neither guideline distinguishes between persons diagnosed in these age groups or persons who age into these groups and now are initiating therapy.

In recent years, a significant change has occurred with respect to timing of initiating antiretroviral therapy in the general population of HIV-infected patients, with a consistent trend favoring initiating therapy earlier in the course of HIV disease. Results from several large cohort studies have

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**Routine Monitoring of CD4 Cell Counts and HIV RNA Levels in HIV and Aging**

- The routine monitoring of CD4 cell counts and HIV RNA levels in patients older than 50 should follow the same general approach recommended for all HIV-infected patients. A CD4 cell count and HIV RNA level should be obtained at the initial evaluation and followed every 3-4 months prior to initiating antiretroviral therapy. Patients initiating antiretroviral therapy should have more intensive monitoring of HIV RNA levels, including a baseline HIV RNA level prior to starting therapy, a follow-up 2-4 weeks after initiating therapy, and continued monitoring every 4-8 weeks until HIV RNA levels become undetectable. Once HIV RNA levels become undetectable, the frequency of monitoring HIV RNA can revert to routine checks every 3-4 months. Monitoring of CD4 cell count and HIV RNA level can be extended to every 6 months in adherent patients who have sustained suppression of HIV and stable clinical status for at least 2-3 years.
strongly suggested a survival advantage with initiation of antiretroviral therapy earlier in the course of HIV disease (Kitahata et al. 2009; Sterne et al. 2009). In addition, growing evidence suggests that uncontrolled HIV produces a “chronic inflammatory state” associated with an increased risk of developing cardiovascular disease (Phillips et al. 2008) and non-AIDS malignancies (Bruyand et al. 2009), and CD4 counts below 500 are associated with higher cardiovascular risk (Lichtenstein et al. 2010), and risk for non-AIDS malignancies (Guiguet et al. 2009). Anti-retroviral therapy results in an improvement in several markers associated with cardiovascular disease and may also reduce the risk of malignancies (OARAC DHHS - 2011).

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**Immunizations in HIV and Aging**

There is a large body of data that vaccine preventable illnesses occur with greater frequency and are more severe in HIV-infected patients than in age-matched control subjects. Thus, a number of vaccines are indicated in HIV-infected subjects.

Consensus is widespread for use of most vaccines in persons living with HIV (PLWH) – these recommendations are nicely summarized in a recent Infectious Diseases Society of America Guideline for Vaccination of the Immunocompromised Host [1]. PLWH should be immunized according to the CDC schedule for adults (Figure 1). Regular primary and booster dose schedules based on age for Td/Tdap, hepatitis A and B, inactivated polio, and human papilloma virus (HPV), as well as annual influenza immunization and combination pneumococcal vaccines are suggested in PLWH (Figure 2). Live-attenuated organism vaccines are generally contraindicated, though in patients with a CD4 count > 200/mm3 mumps, measles and rubella (MMR) and varicella vaccines are indicated in patients not previously immunized. Particular caution should be noted in using yellow fever vaccine for travelers with HIV infection, but immunization can be considered for those at high risk of acquiring the disease during

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**Fig 2** Recommended vaccines based on immunocompromising condition including HIV. From CDC website http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule-bw.pdf
travel if they have asymptomatic HIV and CD4 counts are > 200 mm$^3$.

*Current vaccine efficacy and evidence for a change in vaccine responsiveness with advancing age in PLWH.*

In persons without HIV infection vaccine responsiveness declines with age, but differs by the vaccine. For example, hepatitis B vaccine responses begin to decline around age 35-40, whereas zoster and pneumococcal polysaccharide vaccine (PPV) responses begin waning about age 70-75 years [3]. Do vaccine responses wane at an earlier age in HIV-infected subjects and should this influence the recommended adult immunization schedule? Although data are limited, there is some suggestion that HIV does accelerate and/or enhance age-related declines in vaccine response. Two studies examined PPV and pneumonia prevention in HIV patients using age as a variable. Teshale et al. [5] showed that age 45+ was associated with all cause pneumonia even after adjustment for vaccine status indicating advanced age was associated with poorer vaccine efficacy. However, Rodriguez-Barradas et al. [6] found no such association in the VACS cohort. PPV was protective when pneumonia was examined as an outcome in that study only in HIV-infected subjects (average age 49 years). Efficacy of influenza vaccination in HIV-infected subjects has been examined in a number of studies with response dependent on CD4 count (Figure 3).

There is surprisingly little data on zoster vaccine in HIV-infected subjects despite substantial data on varicella vaccine. An ongoing trial (ClinTrials.gov # NCT00851786) may address this deficiency.
The most extensive examination of age and vaccine response in well-treated HIV-infected subjects was published [4]. Comparing HIV-infected, HAART-treated subjects < 40 (mean 31 yrs) vs. those > 50 (mean 59 years), all subjects had an undetectable viral load for 2 years and CD4 counts > 400. All had been immunized with tetanus toxoid (TT) during childhood, but not since; each subject was given a single TT boost. Age > 50 (Fig. 4) was associated with greatly reduced humoral (serum IgG) and cellular (T cell interferon production) responses after TT immunization. Additional in vitro studies show anti-IL-10 improves responses in aged HIV-uninfected patients, but not HIV-infected aged suggesting the mechanism of vaccine non-response differs. Since TT is a recall response, and naïve responses are more severely affected by age, one would anticipate naïve responses would be similarly, or more severely, reduced.

**New Recommendations for Pneumococcal Immunization for HIV-infected Patients**

The CDC now recommends that all adults aged 19 and older with immunocompromising conditions, which includes HIV, should be immunized. For those PLWH who have not previously received any pneumococcal vaccine one dose of the 13-valent protein-conjugated pneumococcal vaccine (PCV13) should be followed by a dose of pneumococcal polysaccharide vaccine (PPSV23) at least 8 weeks later. If the patient has previously received at least one dose of PPSV23, they should receive a single dose of PCV13 no sooner than 1 year after the last PPSV23 dose. If patients require another PPSV23 dose, it should be administered no sooner than 8 weeks after PCV13 and 5 years after the last PPSV23 dose.

![Figure 3. Seroprotection rate after standard-dose inactivated influenza vaccine (IIV) in Healthy control subjects vs. PLWH stratified by CD4 count at the time of immunization (Reproduced from [7] with permission).](image-url)
Efficacy of High Dose Inactivated Influenza Vaccine (IIV)

A high-dose IIV is available for individuals ≥65 years of age; FDA approval was based on data showing increased immunogenicity of the high-dose vaccine in older adults. A large randomized trial over two flu seasons to examine clinical efficacy was presented at a recent meeting of the Advisory Committee on Immunization Practices (ACIP) (http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-oct-2013/04-Fluzone-Greenberg.pdf). High-dose (60 µg of protein) IIV was compared to standard dose (15 µg protein) IIV for clinical efficacy and had a relative efficacy of 24% (95% CI 9.7%-36.5%) compared with standard dose IIV. There were 227 lab-confirmed cases among the 15,892 participants who got high dose IIV, for a rate of 1.43%, and 300 cases among the 15,911 who received the standard dose IIV, for a rate of 1.83%. This exceeded the FDA-mandated definition required for superiority (lower bound of the 95% confidence interval > 9.1%). No HIV infected patients were knowingly included in this study, but HIV testing was not performed. At this time, however, the ACIP has not stated a preference for high-dose vaccine over the standard dose vaccine in older adults.

In a small clinical trial of HIV-infected patients (n=190) randomized to receive high-dose vs. standard-dose IIV immune responses were superior in the high-dose group, similar to the results noted above for seniors [8]. At this time, however, there is no recommendation to use high-dose IIV in HIV subjects unless they meet the age criteria, over 65, noted in Figure 1.
References


Cigarette smoking is known to be a significant cause of morbidity and mortality in the HIV-noninfected population, and is one of the leading causes of the increase in cardiovascular disease in Western cultures. While about 20% of the general population in the US smokes (CDC 2011), between 39% to 59% of HIV-infected people smoke (Tesoriero et al 2010). There has been a growing incidence of lung cancer among patients (Gritz et al. 2007) with HIV/AIDS. In the ART-era HIV-infected persons who smoke have a lower quality of life and a doubling of their mortality, even when factors such as age, CD4 cell count, HIV RNA level are controlled. Smoking will increase all-cause and non-AIDS related mortality compared to non-smokers. The number of life-years lost due to smoking is higher than those lost to HIV-infection. (Helleberg et al 2013). COPD, atherosclerosis, osteopenia, periodontal disease and human papillomavirus infections are higher in HIV-infected patients who smoke (Shirley et al. 2013). Smoking cessation may ameliorate some of these adverse effects. Nicotine addiction is particularly difficult to treat in the HIV-infected population. Traditional approaches including behavior modification, motivational interviewing techniques, group therapy, nicotine replacement, nicotine receptor-blockade and non-traditional methods such as acupuncture have had various amounts of success. An intensive behavioral approach failed to improve success rates compared with a standard intervention, although patients who were highly motivated and used nicotine replacement therapy were the most successful (Tashima 2009). There may be racial and ethnic differences in response to smoking cessation (Lloyd-Richardson et al. 2008).

Smoking cessation is critical to the management of HIV/AIDS. Healthcare providers need to continue to promote smoking cessation, although this will likely only encourage those with less nicotine dependence. There is a need for more effective smoking cessation strategies for patients with HIV/AIDS. (Harris 2010) There are no specific data on smoking cessation in the older HIV infected population.

References
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A growing body of evidence suggests cardiovascular disease is more frequent in HIV-infected subjects (Klein et al. 2002; Triant et al. 2007). In one study, HIV-infected individuals presenting with acute coronary syndromes were more than a decade younger compared to controls (Hsue et al. 2004). Some evidence suggests this may be associated with specific drugs used to treat HIV such as protease inhibitor therapy (Friis-Møller et al. 2007). However, the effect of antiretroviral therapy is clearly complicated as interruption of antiretroviral therapy was associated with an increased risk of cardiovascular events in untreated HIV patients and associated with treatment interruption (El-Sadr et al. 2006).

Accelerated “aging” in the cardiovascular system. Age is a component of the Framingham Risk Score (FRS) (Wilson et al. 1998) and advanced age is a well-recognized cardiovascular (CVD) risk factor. Whether the “points” awarded in the FRS for age should be modified in HIV-infected patients remains unclear, but there are some data from surrogate marker studies that subclinical CVD occurs more frequently at younger ages when HIV-infection is present. It is unclear whether this is due to HIV itself, anti-retroviral therapy or traditional risk factors. One estimate from studies examining coronary artery calcium deposition (Guaraldi et al. 2009) and some studies examining carotid intima-media thickness (summarized in Maggi et al. 2009) is that average vascular age in HIV-infected patients is approximately 15 years “older” than expected for chronologic age. Taken together these findings may suggest the screening of CVD for HIV-infected individuals should occur at a younger age; however future studies will be needed to further evaluate this concept. Guidelines for screening of CVD in the setting of HIV infection are summarized in the literature and largely follow guidelines for individuals without HIV infection (Hsue et al. 2008).

Specific IDSA/HIVMA guidelines for evaluation and management of dyslipidemia (Figure) have not been updated since 2003 (Dubé et al. 2003) and largely follow the NCEP/ATPIII guidelines. Primary Care Guidelines for HIV-infected patients that included recommendations for CVD/cerebrovascular disease and lipid screening/management were published in 2009 (Aberg et al. 2009).
The following summarizes their recommendations:

- **Serum fasting lipid profile (FLP)**
  - Obtain FLP
    - Obtain every 6-12 months in all HIV-infected patients
    - Obtain FLP 4-6 months after starting anti-retroviral therapy
    - “Consider” FLP within 1-3 months of changing anti-retroviral therapy
    - Dyslipidemia should be managed per NCEP guidelines (www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf) that suggest target levels for dyslipidemia management for those with and without CAD equivalents (i.e. diabetes mellitus, aortic aneurysm, peripheral vascular disease, symptomatic CAD, transient ischemic attack or stroke, and 10-year risk for CAD > 20% by Framingham criteria).

- **Other CVD risk factor screening**
  - Blood pressure check in all patients annually

- **Whether or not HIV infection should be considered a risk equivalent similar to DM is not known but may be a possibility in the future which would imply lower BP guidelines and LDL cholesterol targets.**

*Managing Risk for Transient Ischemic Attack (TIA) and Cerebrovascular Accident (CVA)*

While an elevated but small CVA risk was noted prior to the era of effective ART, preventive management of CVA currently has taken on a prominent focus for older HIV infected patients.

![Figure 1](image-url)
Although uncommon (0.5–7%) prior to effective ART, CVA was nevertheless found at a higher-than-expected rate (10–25 per 100,000), controlling for age (Berger et al. 1990). Both small vessel disease, which would be consistent with HIV-associated neurocognitive impairment without focal neurological findings, and large vessel disease, which would be consistent with focal neurological findings as well as neurocognitive impairment, are involved. Both contribute to the vasculopathy associated with aging and HIV infection. In one population-based retrospective study of the pathogenic mechanisms of CVA among 82 HIV infected patients, cardioembolism accounted for 18%, as did small vessel disease, followed by large vessel disease (12%), vasculitis (13%) and hypercoagulability (9%) (Ortiz et al. 2007). The results on CVA risk have become increasingly notable over time and support the conception of HIV infection in the era of effective ART as an inflammatory disease that continues in the face of effective ART.

As with HIV-uninfected patients, cardiomyopathy represents an additional CVA risk factor. One 4-year observational study of 296 pts with a spectrum of HIV-associated illnesses before the initiation of effective ART found that 15% had a dilated cardiomyopathy with global left ventricular hypokinesis (Currie et al. 1994). The incidence was strongly associated with CD4 count of less than 100 cells/mm³. Atrial fibrillation and HIV-associated dilated cardiomyopathy were examined in one recent study of HIV and CVA but were found to be similarly frequent in a group with ischemic stroke (n = 17) and a group without stroke (n = 99) (Ekpebegh et al. 2011) (Longo-Mbenza et al. 2011). Thus, while atrial fibrillation is common in HIV-associated dilated cardiomyopathy, the specific relationship of CVA to atrial fibrillation, while expected, remains unclear in HIV infection. Related to this issue, interactions between ARVs and oral anticoagulants represent an issue in the current treatment of thromboembolism in the HIV infected. To date, nine case reports documenting drug interactions between oral anticoagulants and ARVs have been reported (Goldstein 2008) conducted a retrospective analysis of these cases and found that, the median percentage of INR measurements of blood clotting time in the therapeutic range was 28.6%. Of those outside the range, 50.5% were sub-therapeutic and 21.2% were supra-therapeutic. It might be concluded that a heightened awareness of the potential difficulty in achieving adequate anti-coagulation in HIV infected patients on effective ART is warranted.

References


The incidence of type 2 diabetes mellitus is reported to be as much as four times higher in HIV-infected patients compared to uninfected patients and increases with increasing age. The incidence of the metabolic syndrome is higher. The increase in risk in ART-treated patients may be related to the use of certain antiretroviral drugs, such as thymidine analogues and protease inhibitors (Llibre et al. 2009; De Wit et al. 2008), obesity, hepatitis C coinfection. It appears that the new protease inhibitors and newer classes of antiretroviral drugs do not promote glucose intolerance (Rasmussen et al. 2012).

Prevention of diabetes is similar to the approach in uninfected older patients, focusing on lifestyle changes such as weight loss, aerobic exercise and proper diet. Screening for glucose intolerance should be performed regularly, before and after initiation of ART (Simone & Appelbaum 2008). There is some debate on whether screening should be done with fasting blood glucose levels (FBG) or using glycated hemoglobin. The American Diabetes Association has recommended that glycated hemoglobin is an acceptable screening tool, with a diagnosis of diabetes when the glycated hemoglobin is equal to or greater than 6.5% (American Diabetes Association, 2014). However, studies have shown that while this test is highly specific, it is insensitive and should be combined with FBG (≥ 126) for screening (Eckhardt 2011).

Management of patients may include switching to less glucose intolerant antiretroviral drugs and using the American Diabetes Association guidelines. This includes the use of oral hypoglycemic agents and insulin. The target glycated hemoglobin should be increased to 8% for frail patients, especially if their life expectancy is less than 5 years, are at high risk for hypoglycemia, polypharmacy or drug interactions (Reuben 2013).

Recent studies have shown no benefit and possible harm from tight glucose control in type 2 diabetes mellitus (Wilson 2011). The glycated hemoglobin should be checked at least twice yearly. Care of HIV infected diabetics should focus on prevention of complications (such as foot ulcers, neuropathy, retinopathy, and nephropathy).
retinopathy, hypertension and vascular disease) as much as with HIV-uninfected patients. Renal function and presence of proteinuria should also be carefully monitored as both diabetes and HIV increase the risk. There is increasing prevalence of obesity in the older population (American Geriatrics Society, 2013) and since obesity is a risk factor for development of the metabolic syndrome and hyperglycemia, clinicians should counsel their older patients with HIV to maintain proper BMI.

Morphologic changes are common in older patients with HIV/AIDS. Increasing age is risk factor for loss of subcutaneous fat (lipodystrophy) and/or increase in central fat deposition (lipohypertrophy). Management options include switching ART (removing thymidine analogues, using NNRTIs or INSTIs), surgical removal of fat, use of growth hormone or analogues.

References:


The prevalence of disease and comorbidities increases with advancing age, and along with this process, come additional medications to treat comorbidities. Treatment of these medical problems may require the patient to see providers in specialty clinics or be hospitalized and medications initiated while hospitalized. For these reasons, the primary care provider is highly encouraged to perform annual medication reconciliation so that a complete and active medication list is available. This process isn’t complete until the prescriber discontinues medications no longer indicated and notifies the dispensing pharmacy and patient thus reducing risk for toxicity and/or drug-drug interactions.

To assist with the medication reconciliation and assessment, it is recommended to utilize a validated instrument such as Beers list or STOPP in evaluating potentially inappropriate prescribing.

To reduce the risk of polypharmacy, it is recommended that patients utilize one pharmacy or a pharmacy with an integrated pharmacy computer network and where possible, utilize an HIV specialty pharmacy.

For patients with renal insufficiency, the Cockcroft-Gault derived creatinine clearance calculation should be used to determine the appropriate medication dose or frequency adjustments. While less accurate in older patients, this equation is still widely used in renal dosing charts, by the FDA and within package inserts. However, the renal function estimated by MDRD if unadjusted for body surface area may also be a reasonable substitute.

In the setting of hepatic dysfunction, certain medications need dose adjustment.

*Drug-drug Interactions and Polypharmacy in HIV and Aging*

- The primary care provider is highly encouraged to perform annual medication reconciliation and a medication review at every visit so that a complete and active medication list is available. This process isn’t complete until the prescriber discontinues medications no longer indicated and notifies the dispensing pharmacy and patient thus reducing risk for toxicity and/or drug-drug interactions.
- To assist with the medication reconciliation and assessment, it is recommended to utilize a validated instrument such as Beers list or STOPP in evaluating potentially inappropriate prescribing.
- To reduce the risk of polypharmacy, it is recommended that patients utilize one pharmacy or a pharmacy with an integrated pharmacy computer network and where possible, utilize an HIV specialty pharmacy.
- For patients with renal insufficiency, the Cockcroft-Gault derived creatinine clearance calculation should be used to determine the appropriate medication dose or frequency adjustments. While less accurate in older patients, this equation is still widely used in renal dosing charts, by the FDA and within package inserts. However, the renal function estimated by MDRD if unadjusted for body surface area may also be a reasonable substitute.
- In the setting of hepatic dysfunction, certain medications need dose adjustment.

Polypharmacy is estimated to occur in 20-50% of patients, with adverse drug reactions more common and serious in the older patient (Kennerfalk et al. 2002; Pizzuti et al. 2006). It is has been recently estimated that 100,000 emergency hospitalizations were due to medications with 1.5% of these occurring in the elderly (Budnitz DS 2011). While age alone has little impact on organ reserves or capacity, comorbidities play a larger (Herrlinger & Klotz 2001; Klotz 2009). As a result, it is important to recognize that chronological age may not always correlate to biological age. To reduce the risk of polypharmacy it is recommended, where possible, that the patient utilize one pharmacy, preferably one with experience caring for HIV-infected patients or one that has an integrated pharmacy computer network. Utilizing a specialty pharmacy has been shown to improve HIV care in terms of fewer contraindicated medications and improved adherence (Hirsch et al. 2009). Additional benefits may also include improved pharmacist-prescriber communication regarding clinically significant drug-drug interactions, medication reconciliation needs, monitoring adherence, and providing adherence aids such as Medi-Sets/pillboxes, medication delivery and personalized patient counseling. Patient preference is important in assessing the benefits and risk of additional meds. Some patients are bothered by taking many medications while others are not.

Recently, more data has become available describing polypharmacy related issues in the HIV-infected population. In a cross-sectional analysis of the Veterans Administration electronic medical and pharmacy records from October 2009 to September 2010, 16,989 HIV-infected patients receiving antiretroviral therapy and 47,613 HIV-uninfected patients were identified and assessed for polypharmacy (Edelman 2013). For both the HIV-infected patients and controls, mortality was greater with a higher number of medications, particularly in those who took ≥5 medications. For HIV-infected patients receiving 3-4 medications, 5-7 medications, and 8 or more medications, hazard ratios for mortality were approximately 1.4, 2.1, and 2.1, respectively, while for controls they were 1.4, 1.5, and 1.9, respectively. The association between polypharmacy and increased mortality is concerning. In addition, data from the HOPS cohort indicated that in patients 50 years and older, 54% of patients experienced polypharmacy compared to 34% of patients less than 50 years old (Holtzman C 2013). At this point, tools are needed for clinicians to use to assess and reduce polypharmacy.

Table 1: Common Medications Requiring Renal Dose Adjustment

<table>
<thead>
<tr>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
</tr>
<tr>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
</tr>
<tr>
<td>Fluconazole</td>
</tr>
<tr>
<td>Gabapentin</td>
</tr>
<tr>
<td>H2-antagonists</td>
</tr>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Nucleoside RTIs</td>
</tr>
<tr>
<td>except abacavir</td>
</tr>
<tr>
<td>Valacyclovir</td>
</tr>
</tbody>
</table>

Assessing and Evaluating Polypharmacy
Both the Beers criteria (Beers MH 1997, American Geriatrics Society 2013) and the STOPP (Screening Tool of Older Person's Prescriptions)(Gallagher P et al. 2008) are two validated instruments that can be used to reduce potentially inappropriate medications in older adults that have been associated with increased morbidity or mortality in older patients. While both tools are available online with the explicit criteria and are too long to be listed here, the Beers criteria tends to focus on potentially inappropriate medications in older adults while the STOPP criteria focuses on potentially inappropriate medication-disease combinations. Examples of medications on the Beers criteria include use of first generation antihistamines, benzodiazepines and tricyclic antidepressants to name a few. Examples of STOPP criteria that may be encountered in clinic include use of thiazide diuretics and gout, use of scheduled opiates without a bowel stimulant or the use of a non-steroidal anti-inflammatory agent in patients with renal disease, moderate to severe hypertension or those with a history of peptic ulcer bleeding or GI bleeds. Out of 600 patients 65 years and older, STOPP criteria identified 329 adverse drug events in 158 patients. Sixty-seven percent were identified as being a factor in hospital admission and 69% were considered avoidable (Hamilton et al. 2011). Much more research needs to be performed in this field and efforts to reduce polypharmacy need to be implemented in the HIV infected population. Clinical pharmacists can serve a key role in optimizing patient care by applying Beers and/or STOPP criteria in their annual review of patient medication regimens.

**Pharmacokinetic and pharmacodynamics changes**

The difficulty with determining drug-drug interactions is that the studies are traditionally, done in young and healthy volunteers and less commonly, in HIV-infected volunteers. This is done to minimize any potential confounders due to age, reduced renal or hepatic function, concomitant medications and co-morbidities. The true extent of a drug interaction in an older patient may never be able to be fully assessed due to these reasons. Therefore, we must extrapolate from the available data and assume that the

| Table 2: Medications Associated with Increased Likelihood of Toxicity |
|---------------------------|--------------------------|
| Medication                | Suggested Management    |
| Antiemetics              | Use with Caution         |
| Antispasmodics           | Use with Caution         |
| Antidepressants          | Use with Caution         |
| Alpha-blockers           | Use with Caution         |
| Beta-blockers            | Use with Caution         |
| Benzodiazepams           | Should be Avoided        |
| (diazepam, chlordiazepoxide, alprazolam) |
| Beta-agonists            | Should be Avoided        |
| Diphenhydramine          | Should be Avoided        |
| Doxepin                  | Use with Caution         |
| Fentanyl, oxycodone, morphine, methadone |
| Meperidine               | Should Be Avoided        |
| Muscle Relaxants         | Use with Caution         |
| (carisoprodol, methocarbamol, baclofen) |
| Sedative hypnotics       | Should be Avoided        |
| (zolpidem, others)       |                          |
| Temazepam, lorazepam     | Should be Avoided        |
| Tricyclic antidepressants| Should be Avoided        |

Both the Beers criteria (Beers MH 1997, American Geriatrics Society 2013) and the STOPP (Screening Tool of Older Person's Prescriptions)(Gallagher P et al. 2008) are two validated instruments that can be used to reduce potentially inappropriate medications in older patients that have been associated with increased morbidity or mortality in older patients. While both tools are available online with the explicit criteria and are too long to be listed here, the Beers criteria tends to focus on potentially inappropriate medications in older adults while the STOPP criteria focuses on potentially inappropriate medication-disease combinations. Examples of medications on the Beers criteria include use of first generation antihistamines, benzodiazepines and tricyclic antidepressants to name a few. Examples of STOPP criteria that may be encountered in clinic include use of thiazide diuretics and gout, use of scheduled opiates without a bowel stimulant or the use of a non-steroidal anti-inflammatory agent in patients with renal disease, moderate to severe hypertension or those with a history of peptic ulcer bleeding or GI bleeds. Out of 600 patients 65 years and older, STOPP criteria identified 329 adverse drug events in 158 patients. Sixty-seven percent were identified as being a factor in hospital admission and 69% were considered avoidable (Hamilton et al. 2011). Much more research needs to be performed in this field and efforts to reduce polypharmacy need to be implemented in the HIV infected population. Clinical pharmacists can serve a key role in optimizing patient care by applying Beers and/or STOPP criteria in their annual review of patient medication regimens.
Table 3: Common Medications Interacting with Antiretrovirals

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azole antifungals (esp. itraconazole,</td>
<td>Flucytosine</td>
</tr>
<tr>
<td>posaconazole, voriconazole)</td>
<td>H2-antagonists (when combined with atazanavir</td>
</tr>
<tr>
<td></td>
<td>or rilpivirine)</td>
</tr>
<tr>
<td>HCVNS/4A inhibitords (boceprevir,</td>
<td>PDE5 inhibitors (esp. tadalafil)</td>
</tr>
<tr>
<td>telaprevir)</td>
<td>Proton pump inhibitors (when combined with</td>
</tr>
<tr>
<td></td>
<td>atazanavir or rilpivirine)</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Statins (esp. lovastatin and simvastatin)</td>
</tr>
<tr>
<td>Wafarin</td>
<td></td>
</tr>
</tbody>
</table>

Despite its shortcomings, the Cockcroft-Gault equation is still primarily used by the FDA, product package inserts and guidelines when drug dosing guidance is needed. This document recognizes that many labs provide an eGFR rather than a creatinine clearance based on Cockcroft-Gault. Since many aging patients may already have some level of chronic kidney disease, the eGFR derived from the MDRD equation may be used to facilitate renal dosing of medications as long as it is unadjusted for body surface area. Common medications requiring renal dose adjustment include acyclovir, fluconazole, gabapentin, H2-antagonists and most nucleoside RTIs (Table 1). Meperidine should be avoided in patients with renal insufficiency as should most non-steroidal anti-inflammatory agents. In addition, non-steroidal agents are associated with an increased risk of gastrointestinal bleeding. For HIV infected patients, preliminary studies suggest that tenofovir requires closer monitoring in an older individual than in a younger cohort (Goeddel et al. 2010).

Pharmacodynamic differences predispose patients to more adverse drug reactions. This is attributable to enhanced sensitivity to centrally and peripherally mediated anticholinergic side effects (e.g. tricyclic antidepressants, diphenhydramine, doxepin, muscle relaxants, antiemetics, antispasmodics, antidepressants), reduced benzodiazepine clearance (e.g. chlordiazepoxide, diazepam), decreased baroreceptor responsiveness (alpha-blockers, beta-blockers, beta-agonists) and increased CNS sensitivity to opioids and sedative-hypnotics (see Table 2). Caution should be used when prescribing and monitoring anticoagulation therapy and antipsychotics should not be used to treat insomnia or other non-approved indications. Additional medications that serve as markers for increased potential for interactions and adverse drug events in the HIV infected population include ritonavir-booster protease inhibitors, statins, tenofovir, H2-antagonists and proton pump inhibitors (see Table 3) (Kennerfalk et al. 2002; Pizzuti et al. 2006; Tommasi et al. 2010) that more unusual adverse drug reactions may be seen.

While little evidence exists for medication dosing based on concentrations in an older HIV infected population, the clinician must rely on data from the uninfected population in addition to screening for high alert medications on the patient’s medication list to reduce the likelihood of a medication induced reaction made more likely due to altered...
Hepatic dysfunction

Not only does the clinician need to consider renal dysfunction, but also hepatic function in the correct dosing of medications. Hepatic dysfunction, while it can occur in co-infected individuals, is not limited to that population but also in patients with other forms of dysfunction such as those caused by alcoholic cirrhosis, etc. Medications that are hepatically metabolized may accumulate to supratherapeutic concentrations in patients with hepatic dysfunction. The risk of toxicity can be reduced by dose adjustment. Rather than utilizing transaminases to determine hepatic dysfunction, hepatic function is best measured by the use of the Child-Pugh score which should be calculated and utilized to determine the proper medication dose.

Antiretrovirals that require dose adjustment based on hepatic function include abacavir, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Specific dosing information for antiretrovirals as well as details on calculating a Child-Pugh score can be found in the DHHS Guidelines for the Use of Antiretroviral Agents. For the most up-to-date information and for non-antiretroviral medications, the clinician is strongly advised to consult a clinical pharmacist to determine the necessity, and if needed, proper dose of medications for patients with hepatic dysfunction.

For additional information on drug-drug interactions, providers are advised to utilize the tables in the DHHS Guidelines for the Use of Antiretroviral Agents or the CDC/NIH Guidelines for the Prevention and Treatment of Opportunistic Infections. More updated information in an interactive format may be found at University of California San Francisco, HIVInSite Database of Antiretroviral Drug Interactions (http://arv.ucsf.edu) or the Toronto General Hospital Immunodeficiency Clinic Drug Interaction Tables (http://www.hivclinic.ca/main/drugs_interact.html). For additional information on renal dosing, the DHHS guidelines provide a valuable reference for medication dosing in settings or renal or hepatic dysfunction.

References


Oyen, N.F. et al., 2010. Comparisons of sexual behaviors and STD prevalence among older and younger individuals with HIV infection. AIDS care, 22(6), pp.711-7.


Cancer in HIV and Aging

- As part of general health maintenance practices, cancer screening in clinically stable HIV-infected patients 50 years and older should be in accordance to current guidelines for the general population.
- For cervical cancer, anal cancer and liver cancer where HIV-specific recommendations exist, these guidelines should be followed.
- For all patients, providers should take into consideration functional status and life expectancy in applying these treatment strategies.

Non-AIDS cancers increasing cause of mortality among HIV-infected persons

Several lines of evidence indicate that cancer, especially non-AIDS-defining cancers (NADCs), has become an increasing cause of mortality in the HAART era. The risk of a particular cancer varies widely by HIV status.

The results of a prospective, multicenter, observational cohort study of subjects in the HIV Outpatient Study treated from 1996 through 2004 showed all-cause mortality among HIV-infected persons in the United States decreased by almost 80%. Deaths due exclusively to non AIDS-defining illnesses (NADIs) rose from 13.1% to 42.5% in 2004. In the study, the most common cause of NADIs were cardiovascular, hepatic disease, pulmonary disease, and non-AIDS malignancies at 23.5% each (Palella et al. 2006).

More recently, a retrospective review of all causes of mortality in HIV-infected individuals in the Europe and North America from 1996 through 2006 in 13 HIV-1 cohorts participating in the Antiretroviral Therapy Cohort Collaboration (ART-CC) found that of 1597 deaths among 39,272 patients studied and 154,667 person years of follow-up, 49.5% were due to AIDS and 50.5% were due to non-AIDS associated causes. The most frequent non-AIDS causes of death were non-AIDS malignancy (11.8%) followed by non-AIDS infection (8.2%), cardiovascular disease (7.9%), violence (7.8%), and liver disease (7.1%). The proportion of deaths due to AIDS-defining cancers decreased from 20.5% to 12.5%, and that due to non–AIDS-defining cancers increased from 7.3% to 15.4% over the study periods (“Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies.” 2010).

Similarly, the Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study Group observed 2482 deaths in 180,176 person-years (PY) on 33,308 individuals and found that among primary causes of death, NADIs were more common that AIDS-related causes (n=916 vs. 743) (Smith et al. 2010). The main non-AIDS related causes were liver-related (n=341), CVD-related (n=289), and non-AIDS malignancy (n=286).
**Increasing incidence of cancer among HIV-infected persons compared to HIV-uninfected**

Data on increased incidence of non-AIDS-defining cancers in HIV-infected individuals the HAART era compared to HIV-uninfected persons has been mixed but increasingly support this notion. A review of the literature by Chiao et al. found that there was a statistically significant increase in the age standardized incidence ratio (SIR) of several non-AIDS-defining malignancies for HIV-infected persons compared with HIV-uninfected cohorts (Chiao & Krown 2003). In particular, Hodgkin lymphoma, anal cancer, soft tissue cancer, and multiple myeloma, were found to have statistically significant increased SIRs in five large published studies that were reviewed (Frisch et al. 2000; Frisch et al. 2001; Gallagher et al. 1999; Grulich et al. 1999; Serraino et al. 2000). No studies found significant increases in breast cancer, colon cancer, or prostate cancer. In addition, some studies have suggested an increased incidence of invasive cervical cancer in HIV-infected women compared to HIV-uninfected persons, (Frisch et al. 2000) (Serraino et al. 1999) although this may have diminished in the HAART era and with aggressive cancer screening (Massad et al. 2009). More recently, a meta-analysis of the incidence of non-AIDS-defining cancers in HIV-infected individuals demonstrated that among 4797 non-AIDS cancers that occurred among 625,716 HIV-infected individuals, HIV-infected persons were twice as likely to develop a non-AIDS-defining cancer as the general population (Shiels et al. 2009).

**Most Frequent Sites of non-AIDS malignancies**

In the meta-analysis, HIV-infected individuals were shown to be particularly at risk for cancers associated with infections (including anal, vaginal, penile, nasopharyngeal, laryngeal, and oral cancers related to human papilloma virus; liver cancer from the hepatitis B and C viruses; and nasopharyngeal cancer and Hodgkin lymphoma associated with Epstein-Barr virus) and smoking (including lung, kidney, stomach, laryngeal, and oral cancers). Prostate and breast cancer were less common in HIV-infected persons (Shiels et al. 2009). A table of the relative SIRS for HIV-infected persons compared to the general population is below.

<table>
<thead>
<tr>
<th>Site</th>
<th>Studies</th>
<th>Cases</th>
<th>SIR</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>13</td>
<td>847</td>
<td>2.6</td>
<td>2.1 to 3.1</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>13</td>
<td>643</td>
<td>1.1</td>
<td>0.88 to 1.6</td>
</tr>
<tr>
<td>Anus</td>
<td>8</td>
<td>253</td>
<td>2.8</td>
<td>2.1 to 3.5</td>
</tr>
<tr>
<td>Colorectal</td>
<td>4</td>
<td>174</td>
<td>1.1</td>
<td>0.69 to 1.7</td>
</tr>
<tr>
<td>Liver</td>
<td>11</td>
<td>171</td>
<td>5.6</td>
<td>4.0 to 7.7</td>
</tr>
<tr>
<td>Melanoma</td>
<td>10</td>
<td>161</td>
<td>1.2</td>
<td>0.88 to 1.6</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>7</td>
<td>160</td>
<td>3.5</td>
<td>1.8 to 6.8</td>
</tr>
<tr>
<td>Prostate</td>
<td>9</td>
<td>159</td>
<td>0.69</td>
<td>0.55 to 0.86</td>
</tr>
<tr>
<td>Female breast</td>
<td>11</td>
<td>142</td>
<td>0.74</td>
<td>0.56 to 0.97</td>
</tr>
<tr>
<td>Kidney</td>
<td>9</td>
<td>109</td>
<td>1.7</td>
<td>1.3 to 2.2</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>3</td>
<td>108</td>
<td>1.9</td>
<td>1.4 to 2.6</td>
</tr>
<tr>
<td>Leukemia</td>
<td>10</td>
<td>102</td>
<td>2.6</td>
<td>1.9 to 3.5</td>
</tr>
<tr>
<td>Stomach</td>
<td>11</td>
<td>96</td>
<td>1.7</td>
<td>1.2 to 2.5</td>
</tr>
<tr>
<td>Testis</td>
<td>8</td>
<td>96</td>
<td>1.4</td>
<td>1.1 to 1.9</td>
</tr>
<tr>
<td>Lip, oral, and pharynx</td>
<td>2</td>
<td>84</td>
<td>2.2</td>
<td>1.0 to 4.7</td>
</tr>
<tr>
<td>Brain</td>
<td>9</td>
<td>75</td>
<td>1.8</td>
<td>1.2 to 2.7</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>9</td>
<td>72</td>
<td>2.6</td>
<td>1.5 to 4.5</td>
</tr>
<tr>
<td>Larynx</td>
<td>5</td>
<td>62</td>
<td>1.5</td>
<td>1.1 to 2.0</td>
</tr>
<tr>
<td>Esophagus</td>
<td>8</td>
<td>51</td>
<td>1.5</td>
<td>0.99 to 2.3</td>
</tr>
<tr>
<td>Bladder</td>
<td>9</td>
<td>48</td>
<td>1.1</td>
<td>0.72 to 1.7</td>
</tr>
<tr>
<td>Head and neck</td>
<td>4</td>
<td>42</td>
<td>2.0</td>
<td>1.1 to 3.6</td>
</tr>
<tr>
<td>Pancreas</td>
<td>9</td>
<td>39</td>
<td>1.0</td>
<td>0.74 to 1.4</td>
</tr>
<tr>
<td>Colon</td>
<td>4</td>
<td>26</td>
<td>0.81</td>
<td>0.48 to 1.4</td>
</tr>
<tr>
<td>Vagina</td>
<td>4</td>
<td>25</td>
<td>0.49</td>
<td>0.49 to 1.8</td>
</tr>
<tr>
<td>Thyroid</td>
<td>6</td>
<td>24</td>
<td>1.1</td>
<td>0.56 to 2.3</td>
</tr>
<tr>
<td>Penis</td>
<td>4</td>
<td>16</td>
<td>6.8</td>
<td>4.2 to 11</td>
</tr>
<tr>
<td>Rectum</td>
<td>2</td>
<td>16</td>
<td>1.5</td>
<td>0.54 to 4.2</td>
</tr>
<tr>
<td>Ovary</td>
<td>6</td>
<td>14</td>
<td>1.4</td>
<td>0.78 to 2.4</td>
</tr>
<tr>
<td>Uterus</td>
<td>4</td>
<td>14</td>
<td>1.5</td>
<td>0.68 to 3.4</td>
</tr>
<tr>
<td>Small intestine</td>
<td>3</td>
<td>10</td>
<td>2.2</td>
<td>1.4 to 3.3</td>
</tr>
<tr>
<td>Bone</td>
<td>5</td>
<td>7</td>
<td>2.6</td>
<td>1.3 to 5.0</td>
</tr>
<tr>
<td>Eye</td>
<td>2</td>
<td>7</td>
<td>3.1</td>
<td>1.6 to 5.9</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>2</td>
<td>7</td>
<td>4.1</td>
<td>2.1 to 7.9</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>2</td>
<td>3</td>
<td>2.6</td>
<td>1.1 to 6.4</td>
</tr>
</tbody>
</table>

| All non-AIDS cancers  | 9       | 3513  | 2.0  | 1.8 to 2.2 |

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*Table 3: From Shiels MS. A Meta-Analysis of the Incidence of Non-AIDS Cancers in HIV-Infected Individuals. J AIDS:52(5);611-622 by Lippincott Williams & Wilkins. Reproduced with permission of Lippincott Williams & Wilkins in the format Journal via Copyright Clearance Center.*
incident AIDS-defining cancers (ADCs) and non-AIDS-defining cancers (NADCs), rates for most individual infection-related NADCs were significantly elevated in HIV-infected persons, including anal squamous cell, vagina/vulva, Hodgkin’s lymphoma, penis, liver, and HPV-related oral squamous cell cancers (Stein et al. 2001). Infection-unrelated NADCs with increased rates in HIV-infected persons were other anal, non-melanoma skin, other head and neck, lung, and melanoma. Infection-related cancers (ADC and infection-related NADC combined) made up almost 70% of all cancers in HIV-infected persons. HIV-infected persons had more than nine-fold increased risk of infection-related NADC compared with HIV-uninfected persons, mainly in the risk of anal squamous cell cancer and Hodgkin’s lymphoma. HIV-infected persons also had a modest 30% increased risk of infection-unrelated NADC, including a higher risk of other anal, skin, other head and neck, and lung cancers, but lower risk of prostate cancer.

Others have also found that lung cancer was a major non-AIDS-defining cancer early in the HAART era being the most common non-AIDS cancer and the third most common cancer among HIV-infected individuals in the USA, behind Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) (Engels et al. 2006). In the ART-CC study cohort, the most frequent sites for non-AIDS malignancies were respiratory tract or intrathoracic organs (36.7%); digestive organs and peritoneum (28.7%); lip, oral cavity, and pharynx (6.0%); and skin (4.7%) (“Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies,” 2010). However, a recent study of skin cancer suggested that the higher risk of melanoma for HIV-infected persons was more likely due to confounding by sun exposure or perhaps increased medical surveillance than as a result of immunosuppression (Lanoy et al. 2009) and other recent studies found no increased risk (Lanoy et al. 2010).

**Increased virulence of cancers among HIV-infected persons**

In 2003, (Chiao & Krown 2003) noted that compared with HIV-uninfected patients, some malignancies tend to be of higher grade and present with a more aggressive clinical course in HIV infected patients (Chiao & Krown 2003). Some studies have shown that HIV-infected women with invasive cervical cancer are more likely to present with advanced clinical disease, to have persistent or recurrent disease at follow-up, a shorter time to recurrence, a shorter survival time after diagnosis, and are more likely to die of cervical cancer (Frisch et al. 2000; Holmes et al. 2009; Logan et al. 2010). Other studies have shown that HIV-seropositive individuals with hepatocellular carcinoma are younger and more frequently symptomatic and infected with HCV or HBV than HIV-uninfected persons individuals, although tumor staging and survival were similar (Bräu et al. 2007).

As discussed by Shiels (Shiels et al. 2011) HIV-infected individuals may have more virulent cancers because: 1) their depressed immune system is less able to fight oncogenic insults, and /or 2) behaviors of HIV-infected individuals expose them to higher levels of carcinogens such as higher levels of exposure to tobacco smoke, HPV, and others. Finally, a recent report from Italy showed that from 1999–2006 the risk of death from non–AIDS-defining cancers was 6.6-fold higher among Italian people with AIDS than in the general population, being particularly elevated for virus-related cancers (Zucchetto et al. 2010).
Role of Increasing Age in cancer risks among HIV-infected persons

As with the general population, older age has been associated with increased risks on non-AIDS-defining cancers in HIV-infected individuals. In the ART-CC study, older age was strongly associated with increased rates of non-AIDS malignancy (HR per 10 years, 2.32) (“Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies..” 2010). Similarly, in the D:A:D study, older age was associated with an increased risk of death from all causes considered, with the strongest associations for deaths due to non-AIDS malignancies and CVD-related causes (Smith et al. 2010). In an analysis of the SMART study, cancer rates were compared between the subjects continuously taking ART and those that intermittently took ART. AIDS-defining cancer rates were higher in this latter group while NADCs were similar between groups. In this study, age was also a predictor of non-AIDS-defining cancers with an HR of 2.2 per 10 years older (Silverberg et al. 2007).

Current cancer screening guidelines for HIV-seropositive patients

Given the higher rate and virulence of some cancers among HIV-infected individuals, consideration must be given to distinct cancer screening guidelines for HIV+ individuals. These guidelines should be individualized for patients since life expectancy rather than strict age cutoffs are better determinates of the usefulness of cancer screenings.

Cervical Cancer. The US Preventive Services Task Force (USPSTF), the Centers for Disease Control and Prevention (CDC) and HIV Medicine Association (HIVMA) of the Infectious Disease Society of America (IDSA) recommend that HIV-infected women should receive a Pap smear upon starting care and again in 6 months; if both tests are unremarkable, then the woman only needs to be screened annually thereafter (Aberg et al. 2004). Women with atypical squamous cells including ASC-US (atypical squamous cells of unknown significance) and ASCH (ASC cannot rule out high-grade squamous intraepithelial lesion or SIL); atypical glandular cells; low-grade or high grade squamous intraepithelial lesion; or squamous carcinoma noted by Pap testing should undergo colposcopy and directed biopsy, with further treatment as indicated by results of evaluation (Aberg et al. 2004). Despite these recommendations and the increased risk of cervical cancer, ~20% of HIV-seropositive women don’t receive a pap smear within the first year (Kaplan et al. 1999; Logan et al. 2010; Stein et al. 2001) and up to 25% do not receive annual screening (Oster et al. 2009). Increasing age was a risk factor for not getting a pap smear. Yet, among women with HIV in a prospective study that incorporated cervical cancer prevention measures including biannual pap smears, the incidence of invasive cervical cancer (ICC) was not significantly higher than that in a comparison group of HIV-negative women (Massad et al. 2009).

Colorectal Cancer. While, there are no clear evidence that colorectal cancer (CRC) is significantly increased in HIV-infected persons compared to the HIV-uninfected population, CRC is the second leading cause of cancer-related death in the USA. However as HIV-infected individuals live longer, the incidence of colon cancer has been rising (Bedimo et al. 2004). However, HIV-infected individuals were significantly less likely to be up-to-date or to have ever had one or more CRC screening
tests (Reinhold et al. 2005). Current guidelines from multiple sources recommend CRC screening starting at 50 years of age for all persons at average-risk for CRC. In the 2009 update, the USPSTF recommended that adults aged 50 to 74 years (older on case by case basis) be screened in 1 of the following ways: every year with high-sensitivity fecal occult blood testing (FOBT); every 10 years with colonoscopy; or every 5 years with flexible sigmoidoscopy plus interval high-sensitivity FOBT. The American College of Gastroenterology also recently updated their guidelines with specific recommendations (Rex et al. 2009).

**Anal Cancer.** Significantly increased in HIV-infected, with relative risk for developing anal cancer among HIV infected men 37-fold higher than in the general population and 60-fold higher in HIV-seropositive men who had sex with men (Frisch et al. 2000). Although significantly increased in HIV-infected, there are currently no national recommendations on screening for anal cancer although the New York State Department of Health does recommend screening in HIV infected individuals (see Table 2). However, anal cancer screening has been shown to be cost effective in certain models (Goldie 1999). Some advocate screening similar to that of cervical cancer, with annual screening using the Thin-prep solution especially if having ongoing sexual partners. However, additional studies may be warranted – at least larger ecological studies as anal cancer screening is adopted more widely even in the absence of official recommendations.

**Liver Cancer.** Studies have found that HIV-infected individuals develop hepatic cancer at approximately seven times the rate of non-HIV-infected individuals (Patel et al. 2008; Bräu et al. 2007). Screening for hepatic cancer is currently recommended only in patients with cirrhosis, although screening may also be warranted in HBV carriers over 40 years with persistent or intermittent ALT elevation and/or HBV DNA level >2000 (Ghany et al. 2009; Lok & McMahon 2009). This screening involves hepatic ultrasound at 6-12 month intervals (Aberg et al. 2009; Bruix & Sherman, 2005) alpha-fetoprotein (AFP) has poor specificity and sensitivity and its use is currently optional with abnormalities confirmed with liver imaging studies (Kaplan et al. 2009).

**Breast Cancer.** Risks not elevated in HIV. Screening as outlined in HIVMA/IDSA recommendations and others include annual mammograms in all women over 50 years old (every 1-2 years if lifetime risk is <20%). For women 40-49 years old, providers should periodically perform individualized assessment of risk for breast cancer and discuss pros and cons of earlier screening (Aberg et al. 2009).

**Lung Cancer.** Leading cause of cancer-related death in the USA and significantly increased in HIV-infected patients, possibly related to increased smoking in this population. There are no guidelines that support routine screening for lung cancer in HIV-negative or HIV infected individuals. In November 2010, the National Cancer Institute reported that in the National Lung Screening Trial (NLST), a randomized national trial of more than 53,000 current and former heavy smokers ages 55 to 74, there were 20 percent fewer lung cancer deaths among those screened with low-dose helical CT compared to standard chest X-ray. Further analysis will be required to understand this aspect of the findings more fully. There is no data in HIV+ individuals.

**Lymphoma and Multiple Myeloma.** Non-Hodgkin’s lymphoma consistently found to be important non-
AIDS malignancy in HIV-infected patients. No screening recommendations for asymptomatic individuals. Multiple myeloma is rare in HIV but significantly increased risk compared to general population. There are no official recommendations for screening asymptomatic individuals.

**Prostate Cancer.** Risk not elevated in HIV. Screening recommendations are controversial and include annual digital rectal exam and PSA levels in men over 50 years of age; earlier for certain high risk groups such as African Americans. Some guidelines recommend that screenings stop at age 75 or if the patient has less than a 10 year survival.

**Skin Cancer.** The Infectious Diseases Society of America primary care guidelines for HIV-seropositive individuals recommend “special attention to be paid to examination of the skin looking for evidence of seborrheic dermatitis, Kaposi sarcoma, folliculitis, fungal infections, psoriasis, and prurigo nodularis” (Aberg et al. 2009). However, it appears that no guidelines specify the frequency with which HIV-infected patients should be screened for skin cancer.

**Primary CNS Lymphoma (PCNSL):** The incidence of non-Hodgkins lymphoma (NHL) is greatly increased in HIV infected persons. The vast majority are clinically aggressive B cell-derived tumors. The diagnosis of PCNSL is made based upon the presence of malignant lymphocytes within the CNS (typically by biopsy) and by exclusion of systemic disease. PCNSL makes up 15% of NHL in HIV as compared to less than 1% of NHL in the general population (Hull 2009). It is important to conduct an aggressive screening for systemic disease as it has been documented that cases initially presenting as PCNSL may actually be systemic lymphomas when screened more thoroughly(O’Neill et al. 1995). AIDS is the most common disease associated with this tumor. Virtually all PCNSLs in patients with AIDS express EBV-related genomic markers. PCNSL has been reported in 6-20% of patients infected with HIV, and the incidence is expected to rise as patients with low CD4 cell counts survive longer (Ramachandran 2011). Generally, relatively younger age has been associated with the incidence of PCNSL (Obrams & Grufferman 1991) with most patients reported as being in their fourth decade. However, the incidence now appears to be increasing across a wider age range. However older age is associated with decreased survival time in PCNSL. Recently PCNSL has been shown to respond at a high rate to the combination of radiotherapy and chemotherapy in younger patients. This gain has not been generalized to the older patient due to their unlikely candidacy for combined chemotherapy and radiation therapy treatment due to its toxicity. Hence, older HIV infected patients with suspected PCNSL should be considered earlier for brain biopsy for proof of diagnosis (rather than after empirical treatment for CNS toxoplasmosis).

**Conclusion:** HIV-infected individuals may be at increased risk of infection-related non-AIDS defining cancers (NADCs) especially anal, cervical, vaginal, penile, nasopharyngeal, laryngeal, and oral cancers related to HPV; liver cancer from the HBV and HCV; and nasopharyngeal cancer and Hodgkin lymphoma related to EBV. Patients may also be at risk for smoking-related NADCs especially non-melanoma skin, other head and neck, lung, and less likely melanoma
<table>
<thead>
<tr>
<th>Table 2</th>
<th>Screening for HIV-negative</th>
<th>Organization &amp; Year</th>
<th>Guideline HTML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal</td>
<td>No formal guidelines on screening. No organizations endorse screening non-HIV-infected individuals for anal cancer.</td>
<td></td>
<td><a href="http://www.upToDate.com/onlineContent/abstract.do?spid=KeyTurnP#rNw2317&amp;refNum=24.34">http://www.upToDate.com/onlineContent/abstract.do?spid=KeyTurnP#rNw2317&amp;refNum=24.34</a></td>
</tr>
<tr>
<td>Lung</td>
<td>No national guidelines yet.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Breast</td>
<td>Strong consensus: women at average risk: q 1-2 years starting at age 50-69. Less robust consensus: women at average risk: screening 40-49, TP+ using screening mammography. Insufficient evidence to assess the additional benefits and harms of clinical breast examination (CBE) or of digital mammography or magnetic resonance imaging (MRI) instead of film mammography.</td>
<td>USPSTF 2009; Note that ACS, ACR-AMA, NCI, ACOG, NCCN all recommend breast screening starting at 40, while USPSTF and ACP recommend routine screening starting at 50</td>
<td><a href="http://www.uspreventiveservicestaskforce.org/uspstf/uspsbreca.htm">http://www.uspreventiveservicestaskforce.org/uspstf/uspsbreca.htm</a></td>
</tr>
<tr>
<td>CRC</td>
<td>For average-risk individuals beginning at age 50, discontinuation age varies by guideline. USPSTF: FOBT every year; flexible sigmoidoscopy every 5 years; or colonoscopy every 10 years; do not routinely screen 75-84; do not screen over age 85. ACS, MISTF, &amp; ACR: Flexible sigmoidoscopy every 5 years* or Colonoscopy every 10 years, or Double-contrast barium enema every 5 years*; or CT colonography (virtual colonoscopy) every 5 years* are preferred (*** if the test is positive, a colonoscopy should be done). Can also do yearly fecal occult blood test (gFOBT)<em><strong>, or fecal immunochemical test (FIT) every year</strong></em>, or Stool DNA test (sDNA), interval uncertain*** (The multiple stool take-home test should be used. A colonoscopy should be done if the test is positive). Discontinue screening when the individual's estimated life expectancy is less than 10 years.</td>
<td>USPSTF 2008; ACS, MISTF and ACR 2008</td>
<td><a href="http://www.uspreventiveservicestaskforce.org/uspstf08/colostrum.htm">http://www.uspreventiveservicestaskforce.org/uspstf08/colostrum.htm</a></td>
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ACOG - American Congress of Obstetricians and Gynecologists
ACP - American College of Physicians
ACS - American College of Radiology
AMA - American Medical Association
EACS - European AIDS Clinical Society
MISTF - US Multi-Society Task Force on Colorectal Cancer
NCCN - National Comprehensive Cancer Network
NCI - National Cancer Institute
NYS DOH - New York State Department of Health

USPSTF - U.S. Preventive Services Task Force
<table>
<thead>
<tr>
<th>Table 3</th>
<th>Screening for HIV-Positive</th>
<th>Organization &amp; Year</th>
<th>Guideline HTML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Ultrasound +/- AFP; AFP only when ultrasound not available for individuals with chronic liver disease or cirrhosis.</td>
<td>AASLD 2010</td>
<td><a href="http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCVUpdate2015.pdf">Guideline Link</a></td>
</tr>
<tr>
<td>Skin</td>
<td>ACS, Total body skin cancer screening examination as part of periodic health exams at baseline and thereafter as determined by clinician. USPSTF, Insufficient evidence for or against routine screening.</td>
<td>NIA</td>
<td>NIA</td>
</tr>
<tr>
<td>Lung</td>
<td>No national guidelines yet.</td>
<td>NIA</td>
<td>NIA</td>
</tr>
<tr>
<td>Breast</td>
<td>Strong consensus: women at average risk 1-2 years starting at age 50-49, Less robust consensus: women of average risk screening 40-49. To use screening mammography. Insufficient evidence to assess the additional benefits and harms of clinical breast examination (CBE) or digital mammography or magnetic resonance imaging (MRI) instead of film mammography.</td>
<td>NIA</td>
<td>NIA</td>
</tr>
<tr>
<td>CRC</td>
<td>For average-risk individuals beginning at age 50, discontinuation age varies by guideline. USPSTF: FOBT every year; flexible sigmoidoscopy every 5 years, or colonoscopy every 10 years. Do not routinely screen 76-85. Do not screen age 85+. ACS: MSBT, &amp; AGS: Flexible sigmoidoscopy every 5 years, or Colonoscopy every 10 years, or Double-contrast barium enema every 5 years, or CT colonography (virtual colonoscopy) every 5 years are preferred. If the test is positive, a colonoscopy should be done. Can also do yearly fecal occult blood test (FOBT™), or fecal immunochemical test (FIT) every year, or Stool DNA test (sDNA) interval uncertain. The multiple stool antigen home test should be used. A colonoscopy should be done if the test is positive. Discontinue screening when the individual's estimated life expectancy is less than 15 years.</td>
<td>NIA</td>
<td>NIA</td>
</tr>
</tbody>
</table>

ACG - American College of Gastroenterology
AGA - American Gastroenterological Association
ACS - American Cancer Society
AGS - American Geriatrics Society
AMA - American Medical Association
USPSTF - U.S. Preventive Services Task Force
EACS - European AIDS Clinical Society
MSTT - US Multi-Society Task Force on Colorectal Cancer
NCCN - National Comprehensive Cancer Network
NCH - National Cancer Institute
NYSDOH - New York State Department of Health
References:


Hepatitis B virus (HBV), hepatitis C virus (HCV) rates and clinical course among U.S. HIV-seropositives

The rate of HBV and HCV among the HIV-infected individuals in the United States and other Western countries is much higher than that of HIV-uninfected individuals, by some estimates 10-fold higher among HIV-infected individuals (Benito et al. 2005; Soriano et al. 2008). A prevalence study of active and occult HBV infection in a geographically representative HIV-infected US cohort found chronic HBV infection to be present in 7.1% while occult HBV was observed in approximately 10% of HIV-infected patients with HB anticore IgG antibody alone (Shire et al. 2004). By comparison, occult HBV infection has been reported in 0.1–2.4% of HBsAg-negative, anti-HBc-positive (+anti-HBs) blood donors in Western countries such as the United States (Hollinger 2008); although, may be increased by more than two-fold in those with chronic HCV (Cacciola et al. 1999). In a representative cohort of HIV-infected individuals from two large clinical studies of the US Adult AIDS Clinical Trials Group, the overall estimate of HCV prevalence was 16.1%, with significant variability based on risk factors and HIV RNA levels (Sherman et al. 2002). In that study, among patients defined as being “at risk” (e.g. parenteral exposure)
72.7% were HCV positive, whereas among low-risk patients, the seropositivity rate was as low as 3.5%.

**Clinical course among HIV-infected Hepatitis B** and hepatitis C infections are also more virulent in HIV-infected individuals. These infections affect HIV disease progression and/or response to antiretroviral therapy (ART) while HIV infection appears to negatively alter the clinical course of these chronic infections.

**Hepatitis B.** While most HIV-uninfected individuals clear their HBV infection and most with chronic HBV do not develop hepatic complications, the risk of HBV-associated end-stage liver disease and mortality seems to be increased in the setting of HIV coinfection (Konopnicki et al. 2005; Puoti et al. 2002; Soriano et al. 2008). In the Multicenter AIDS Cohort Study (MACS) cohort, an eight-fold increased risk of liver-related mortality was seen among HBV/HIV coinfected compared with HIV-monoinfected individuals (Thio et al. 2002). HBV-HIV coinfection also increases the risk of progression to chronic HBV infection and reduces the rate of spontaneous HBsAg and HBeAg seroconversion (Hadler et al. 1991). Hepatocellular carcinoma (HCC) may also develop at a younger age and be more aggressive in HBV-HIV coinfected individuals (Bräu et al. 2007). The availability of anti-HBV medications may have ameliorated these poor outcomes to some degree.

**Hepatitis C.** Some reports suggest that HCV infection has an effect on HIV disease. These studies have indicated that increased HCV RNA levels were associated with clinical progression to AIDS (Daar et al. 2001); that HCV seropositivity is associated with progression to a new AIDS-defining illness or to death (Greub et al. 2000); and that HCV seropositivity is also associated with a reduced CD4 cell recovery during antiretroviral therapy (Macías et al. 2003). With respect to HCV infection, HIV coinfection has been associated with faster progression to liver fibrosis and cirrhosis (Benhamou et al. 1999; Martinez-Sierra et al. 2003; Soto et al. 1997); higher rates of morbidity and mortality (Bica et al. 2001; Tedaldi et al. 2003) including faster progression to HCC and more aggressive HCC (Bräu et al. 2007); and poorer response to HCV treatment (Chung et al. 2004; Pérez-Olmeda et al. 2003).

**Hepatitis in the elderly HIV-infected population.** Older individuals coinfected with HIV and hepatitis B or C may be at risk for more liver-related complications than younger coinfected individuals. Older age has been a predictor of liver-related complications in HIV-infected individuals. In the D:A:D Study, predictors of liver-related deaths were latest CD4 cell, older age, intravenous drug use, HCV infection, active HBV infection, HIV RNA level, and ART duration (Weber et al. 2006). In addition, age greater than 50 years has been associated with increased rates of hospitalization for liver-related diseases among HIV-infected individuals compared to younger HIV-seropositives (Gebo et al. 2005). Among those with HIV-HCV coinfection, an individual’s age at time of HCV-infection was independently associated with higher liver fibrosis progression rates (Benhamou et al. 1999).

**Current recommendations on hepatitis screening for HIV-seropositive patients:**

**Hepatitis B.** HBV screening is offered to patients with multiple sex partners, MSM, and injection drug users. The Infectious Disease Society of America (IDSA) HIV primary care guidelines recommend that: (i)
HIV-infected patients should be screened for evidence of HBV infection upon initiation of care by detection of hepatitis B surface antigen (HBsAg), antibody to HBsAg, and antibody to hepatitis B total core antigen, (ii) those who are susceptible to infection should be vaccinated against HBV, and (iii) sexual partners of persons who are positive for HBsAg should also be offered vaccination. Patients who are negative for HBsAg and antibody to HBsAg but positive for hepatitis B total core antigen antibody should be screened for chronic occult HBV infection by determination of HBV load by HBV DNA PCR (Aberg et al. 2009). Some argue that screening for occult HBV should be also done testing for HBV DNA with the most sensitive assay available for those with: (i) acute flares of alanine aminotransferase (ALT) that occur during the early phase of therapy for HCV or ALT levels that remain elevated at the end of therapy in biochemical nonresponders should prompt an assessment for occult hepatitis B; (ii) chronic hepatitis C that is hepatitis B core antibody (anti-HBc) positive (+/-anti-HBs at levels of <100 mIU/mL) (Hollinger & Sood 2010).

**Hepatitis C.** The U.S. Preventive Services Task Force (2004) does not support increased screening, based on what it sees as a dearth of evidence of long-term benefits from such screening (USPSTF 2004) recommends against routine screening for hepatitis C infection in asymptomatic adults who are not at increased risk for infection. In addition, they found insufficient evidence for or against routine screening for HCV infection in adults at high risk for infection. Nonetheless, in the past decade, a wide variety of organizations have endorsed increased screening for hepatitis among HIV-seropositive individuals and those at increased risk.

The Centers for Disease Control and Prevention (CDC) recommends routine testing for HCV in patients at increased risk for infection: those who have ever injected illegal drugs, received clotting factors made before 1987, received blood/organs before July 1992, were ever on chronic hemodialysis, or have evidence of liver disease (Alter et al. 2003). The National Institutes of Health (NIH) consensus guidelines are similar to those of the CDC with the exception of recommending screening in those who received blood/organs prior to 1990 (NIH: Management of Hepatitis C 1997).

In the 2009 practice guideline issued by the American Association for the Study of Liver Diseases (AASLD), testing is recommended for (Ghany et al. 2009): (i) those who have injected illicit drugs in the past; (ii) those with conditions associated with a high prevalence of HCV including HIV infection, hemophilia who received clotting products before 1987, persons who were ever on hemodialysis, and those with unexplained abnormal aminotransferase levels; (iii) prior recipients of transfusions or organ transplants before July 1992 including those who were notified that they received blood from a donor who later tested positive for HCV infection, those who received a transfusion of blood/blood products, those who received an organ transplant; (iv) children born to HCV-infected mothers; (iv) healthcare, emergency and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood; (v) current sexual partners of HCV-infected persons.

The Infectious Disease Society of America (IDSA) HIV primary care guidelines recommend that: (i) HIV-infected patients should be screened for HCV infection upon initiation of care by a test for HCV antibody, (ii) positive HCV antibody test results should be confirmed by
measurement of HCV RNA levels by PCR, and (iii) infants born to HCV-positive women should be tested for HCV transmission (Aberg et al. 2009).

In addition to the above screening guidelines, some have suggested that all HIV-infected men who have sex with men (MSM) with unexplained elevated transaminase values should be evaluated for acute HCV infection given the increasing detection of sexually transmitted acute HCV infection in HIV-infected MSM, particularly in association with concurrent sexually transmitted diseases (Browne et al. 2004; Luetkemeyer et al. 2006).

Patients with HBV and/or HCV should receive HAV vaccination (and patients with HCV should also receive HBV vaccination), and should be instructed on avoidance of acetaminophen and alcohol.

References


*Chronic Obstructive Pulmonary Disease in HIV and Aging*

- In the absence of data on the treatment of chronic obstructive pulmonary disease (COPD) specifically in the setting of HIV infection, current therapy of COPD in HIV-infected persons should follow the management guidelines proposed for HIV-uninfected patients. HIV-infected persons have an increased risk for several non-infectious pulmonary conditions including chronic obstructive pulmonary disease (COPD). COPD can present at younger ages in HIV-infected compared to HIV-uninfected patients (Crothers et al. 2011). HIV infection, particularly in the presence of a high viral load, appears to be associated with COPD (Drummond et al. 2011), and lung function decline may be accelerated in patients with high viral load and low CD4 cell counts (Drummond et al. 2013). As in HIV-uninfected persons, cigarette smoking is a major risk factor for COPD among HIV-infected individuals. However, HIV infection is associated with an increased risk for COPD independent of smoking, drug abuse, and opportunistic infections (Crothers et al. 2006; Diaz et al. 2000).

Updated 1/2014

According to the Global Initiative for Chronic Obstructive Lung Diseases, COPD is “characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases” (GOLD 2014). The major risk factor for COPD is cigarette smoking, but occupational and environmental exposures also contribute. Prior bacterial pneumonia and Pneumocystis pneumonia are associated with airflow obstruction on pulmonary function testing (Morris et al. 2000), and may play an important role in the risk and progression of COPD in HIV-infected persons.

COPD can occur at any CD4 cell count or HIV viral load in HIV-infected persons. However, the risk of COPD was increased in HIV-infected persons with a high viral load (>200,000 copies/ml) after adjusting for antiretroviral therapy (ART) use (Drummond et al. 2012). COPD may progress more rapidly in HIV-infected persons with poorly controlled HIV.

Amongst HIV-infected injection drug users, the rate of decline in the forced expiratory volume in one second (FEV1) and the forced vital capacity (FVC) was accelerated in patients with high HIV viral load (defined as >75,000 copies/ml) and with low CD4 cell count (defined as <100 cells/µl), when compared to patients with better controlled HIV disease and to those without HIV infection (Drummond et al. 2013).

The diagnosis of COPD should be suspected in patients who have chronic cough or sputum production, dyspnea, and/or exposure to risk factors for the disease (GOLD 2014). The diagnosis of COPD requires spirometry, preferably with bronchodilator testing to demonstrate fixed airflow obstruction; the definition of fixed airflow obstruction requires that the ratio of
the forced expiratory volume in one second (FEV1) to the forced vital capacity (FVC) be less than 70%, or less than 95% of the lower limit of normal, in association with an FEV1 of less than 80% of predicted (GOLD 2014). Among older patients, using a threshold of the FEV1/FVC of less than 95% of the lower limit of normal is preferred, as this results in fewer false-positive diagnoses of COPD (Hankinson et al. 1999). Screening spirometry to detect COPD in asymptomatic populations is generally not recommended (Lin et al. 2008), although studies have not addressed screening in HIV-infected populations.

In HIV-infected patients with chronic respiratory symptoms, health care providers should obtain spirometry. Complete pulmonary function testing including measurement of diffusing capacity should also be considered, as HIV-infected patients may be particularly likely to have a decrease in diffusing capacity despite relatively normal spirometry (Gingo et al. 2010). Indeed, HIV-infected persons have an increased risk of a low diffusing capacity, defined as <60% predicted normal, compared to uninfected persons after adjusting for smoking and other risk factors (Crothers et al. 2013, Fitzpatrick et al. 2013). A decreased diffusing capacity suggests the presence of emphysema or other disease processes that interfere with normal gas exchange within the lung.

In the absence of data on the treatment of COPD specifically in the setting of HIV infection, current therapy of COPD in HIV-infected persons should follow the management guidelines proposed for HIV-uninfected patients (GOLD 2014, Qaseem et al. 2011). In general, therapy is initiated for symptomatic COPD patients with inhaled bronchodilators. For patients who have regular symptoms and an FEV1<60% of predicted, monotherapy with a long acting inhaled beta-agonist or anticholinergic is recommended; combination therapy may also be considered (Qaseem et al. 2011). Inhaled steroids are generally reserved for patients with more severely impaired lung function (FEV1 less than 50% predicted) and who also have frequent yearly exacerbations (Qaseem et al. 2011).

Special consideration should be given to a few key aspects of COPD management for HIV-infected patients. As with HIV-uninfected patients, smoking cessation should be prioritized. HIV-infected patients should also be monitored for potential complications and interactions between COPD medications and antiretroviral therapy. Protease inhibitors, particularly ritonavir, have been reported to increase systemic levels of inhaled or intranasal fluticasone. Cushing’s syndrome or adrenal suppression may result when corticosteroids are tapered (Soldatos et al. 2005; St Germain et al. 2007). The use of high-dose inhaled corticosteroids also requires careful monitoring, as inhaled corticosteroids are associated with increased risk of oral candidiasis, bacterial pneumonia, (Calverley et al. 2007, Drummond et al. 2008) and tuberculosis (Brassard et al. 2011). The regular use of systemic steroids should preferably be avoided. Given the potential complications associated with steroids, additional studies on the efficacy and/or effectiveness and safety of these medications in HIV-infected persons with COPD are needed.

In addition, COPD is associated with several comorbidities that may particularly complicate care of elderly patients. These include cardiovascular disease, muscle wasting, osteoporosis, malnutrition, depression, anxiety and lung cancer (Nazir & Erbland, 2009). Providers should review vaccination records with their HIV-infected patients to ensure that all patients have
received the recommended pneumococcal and yearly influenza vaccine.

HIV-infected patients with COPD should be considered for participation in pulmonary rehabilitation programs. Lung disease may be an important determinant contributing to poor physical function in HIV-infected persons. Among HIV-infected Veterans, chronic obstructive lung disease (COPD and/or asthma) was among the top comorbid conditions independently associated with self-reported increased physical disability (Oursler et al. 2006). Airflow limitation, as reflected by a low FEV1 is also associated with decreased 6-minute walk distance in HIV-infected patients (Campo et al. 2014, in press).

In studies of HIV-uninfected patients with COPD, physical functioning is significantly improved with participation in pulmonary rehabilitation programs (Nici et al. 2006). In general, pulmonary rehabilitation programs should be prescribed in COPD patients who are symptomatic with an FEV1<50% predicted (Qaseem et al. 2011). Studies support the safety and potential benefit of exercise training in HIV-infected patients (O’Brien et al. 2010) although further studies are needed to determine the role and optimal type of exercise training in HIV-infected patients, particularly older patients with concomitant comorbid diseases such as COPD.

References


Updated 1/2014
*Sexual Health in HIV and Aging*

- Consistent with the primary care guidelines, the health care team should screen older persons at each visit for high-risk behavior or evidence of sexually transmitted diseases, and then provide a tailored prevention message. A more general prevention message should be given at each visit to all patients. Developing a routine way to elicit the patient’s sexual history that avoids judgmental attitudes and asks the patient for permission to discuss sexual function will make it easier to gather the necessary information.

- In HIV discordant couples, there is a special need to emphasize safe sexual practices and full adherence to ART use.

- Use of erectile dysfunction medications or other measures for impotence in men and topical estrogen products for vaginal dryness in women can enhance sexual satisfaction, but care in their use is necessary. The prescription should be linked to specific educational efforts on safe sexual practices.

- PrEP is recommended as one prevention option in those at substantial risk of HIV acquisition for sexually-active adult MSM, for adult heterosexually active men and women, for adult injection drug users and to be discussed with HIV-discordant couples, as an option to protect the uninfected partner.

For those at high risk, sexual behavior has more often been defined through the narrow prism of HIV prevention. But, sexual health is broadly defined as more than just the absence of dysfunction or disease. Sexual health is a significant element contributing to the quality of life of older adults.

There is evidence that positive sexual health protects against those stresses that arise from chronic illness thereby improving health outcomes (Bodenmann 2005). Most recently this observation has been seen to occur in HIV discordant couples (Gamarel et al. 2014). Research supports the view that a gay couple’s sexual health sex life, is a function of the quality of their overall relationship. That relationship, and not social perceptions or approval are correlated with positive sexual satisfaction (Sprecher et al. 2004; Berg et al. 2007). Studies (Trotta et al. 2008) found that about half of those with HIV report sexual problems which include sexual dissatisfaction. Sexual dissatisfaction within couple relationships occurs in the presence of chronic illnesses which in turn reduces personal well-being and health outcomes (Diamond et al. 2012).

Poor quality of life can significantly affect medication adherence as well as patient directed health care decisions that are an integral part of multimorbidity management. Sexual dysfunction can be a side effect of medications, be associated with a past medical/surgical history, or, sexual abuse as well as the oppressive effects of stigma. The successful integration of sexual health care can decrease morbidity and mortality, and enhance well-being and longevity in the patient (Bickley 2008).

Health-care professionals more often underestimate the desire for and level of sexual activity in the older adult population.
thereby neglecting their risk for STI exposure (Lindau et al. 2007). In fact, CDC reports that STI diagnoses in those 65 years and older are increasing and similar to trends in the 20-24-year-old age group (CDC 2013). Quite simply they do not believe that older adults, and especially older adults with HIV, are sexually active. This failure to engage the older adult, and particularly the older adult living with HIV, in a conversation about sexual health and the need for safe sex practices has consequences, which include the spread of HIV. The landmark study by Lindau al. (2007) found that 73% of people aged 57-64 reported having sex in the previous year, as did 53% of those aged 64-75 and 26% of those aged 75-85. Among those who were sexually active, the majority reported having sex two to three times a month. Interest in sex, however does decline with age, especially due to poor health or not having access to a partner. If a person’s health was very good, that person was twice as likely to be sexually active as those in very poor health.

Care providers cannot assume that older adults are not sexually active. They are at risk for STI’s and sexual dysfunction and are likely to feel uncomfortable initiating discussions with their health care provider. By not engaging the older adult, medical care providers have been reinforcing the myth that older adults do not have sex. One of the consequences of this prevailing attitude is that with increasing age the likelihood of having an AIDS diagnosis at the time of initial HIV detection increases (CDC 2011). Primary prevention for HIV and STI’s in older adults should be a priority for the medical team. Unless identified and addressed the sexual health of the older HIV+ patient will have a negative impact on health outcomes. As well, secondary prevention to minimize HIV transmission is needed.

**Sexual Behavior in Older Adults with HIV/AIDS**

Similar to their HIV-negative counterparts, older adults living with HIV are sexually active. Results from a study of almost 1000 persons 50 years and older with HIV in New York City (ROAH: Research on Older Adults with HIV) (Karpiak 2006; Brennan et al. 2009) show that one half of these individuals report sexual activity in the past three months (Golub et al. 2010; Golub et al. 2011). Approximately 75% of older sexually active individuals have sex more than 2 to 3 times per month. They and others (Cook et al. 2010) also found the erectile enhancement drugs did not increase the incidence of unsafe sex practices.

Detailed studies have begun to examine sexual behavior in older adults living with HIV/AIDS (Szerlip et al 2005; Arnten & Klein. 2007; Golub et al. 2010; Golub et al. 2011; Lovejoy et al. 2008; Szerlip et al. 2005; Brennan et al. 2011). The frequency of unprotected insertive sex is high among older adults with HIV. About 41% of the sexually active older adults with HIV in the ROAH Study report unprotected anal or vaginal sex in the past 3 months (Golub et al. 2010; Golub et al. 2011). Different frequencies and patterns of sexual risk behavior have been found among older HIV infected adults by gender and sexual orientation. As an example, older HIV-infected men (regardless of sexual orientation) are more likely to be sexually active compared to women, but condom use rates are lowest among gay and bisexual self-identified males, compared to heterosexuals (Golub et al. 2010; Lovejoy et al. 2008). Studies have also found that older women are at higher risk of STI because of vaginal atrophy that may contribute to increased exposure (Lindau et al. 2007). These older post-menopausal women perceive the elimination of the risk for pregnancy as extending to the elimination of
the risk for STIs including HIV. As older adults living with HIV begin to internalize the emerging consensus that a low or non-detectable viral load is commensurate with low infectivity (but not zero) they are likely to engage in more sexual risk sex behaviors, avoiding the need to disclose their status and not use a condom. Also, reports suggest that for various reasons, older MSM have paired with younger MSM, thereby increasing risk (Mustanski & Newcomb 2013). Such increased behavioral risk needs to be discussed at regular visits with appropriate counseling given (Aberg 2013). However, for persons continuing such behavior referral to a program that offers behavioral modification strategies, including group and phone interventions is needed (Aberg 2013; Illa et al. 2010; Lovejoy et al. 2011) as well as adoption of the daily use of Truvada (CDC 2014).

Primary Prevention Issues (see also Detection and Screening for HIV in Older Adults)

CDC surveillance data (CDC - 2011) show that 17% (1 in 6) of all new HIV infections occur at age 50 and older in the US. That incidence rate has increased from 11% in 2002 (CDC - 2004). Between 30-40% of sexually active HIV infected adults report unprotected anal or vaginal intercourse (Golub et al. 2010 & 2011). Such risk-taking may be associated with less knowledge about HIV/AIDS and recent substance use. Condom use is effective in preventing HIV and STI transmission. However, older persons may not use condoms because they are unaware of the risks. Also, older men can suffer from some degree of erectile dysfunction, which makes condom use less reliable. Topical microbicides for vaginal and anal use by women and men are being developed. A recent clinical trial of pre-exposure chemoprophylaxis (PrEP) with an existing ART in negative MSM subjects found a 44% reduction in the incidence of HIV (Grant et al. 2010). The promise of such regimens is significant but its adoption by at-risk groups is unknown. This finding has been extended to heterosexual men and women, and guidance has been published (CDC 2014). Parallel studies show that treatment of an HIV-infected partner in HIV discordant couples reduces significantly the rates of sexual transmission of HIV (Cohen et al. 2011; CDC, 2014).

Studies consistently demonstrate associations between unprotected sex and negative affect, including depression and anxiety. Research finds high levels of depression, loneliness, anxiety, and chronic stress across gender, race/ethnicity, and sexual orientation among older adults with HIV (Grov et al. 2010; Heckman et al. 2000; Kalichman et al. 2000; Stall et al. 2003) Increasingly, distress and mental health problems are emerging as critical determinants of risk behavior among HIV infected adults.

Most prevention efforts exclusively stress negative psychological factors as predictors of risk behavior. HIV prevention efforts have largely adopted a pathogenic perspective, identifying psychological factors that increase HIV risk behavior. Yet these pathogenic approaches are being reassessed. The use of salutogenic models that engage health promoting factors such as positive psychological functioning (Ryff & Singer 1998) and health behaviors are being assessed (Golub et al. 2011). For the older adult, placing emphasis on positive psychological health factor may represent a better long-term predictor of optimal health outcomes. This approach necessitates that health care providers acknowledge the psychological resources of their clients many of whom are long-term HIV survivors exhibiting a high level of resiliency.
How to Talk to Older Adults about Sexual Health

The following are examples of elements of social and psychosocial assessment (Nusbaum & Hamilton 2002) that can assist in creating a setting where patients feel comfortable expressing the details of their sexual health:

- Do you have any questions or concerns about your sexual functioning? (open ended question)
- Have you noticed any problems or changes with your ability to have or enjoy sex?
- Has your present illness (or medications) affected your sexual function?
- Do you ever have pain with intercourse?
- **Women:** Do you have any difficulty achieving orgasm?
- **Men:** Do you have any difficulty obtaining and maintaining an erection? Difficulty with ejaculation?
- Do you have, or have you ever had, any risk factors for HIV? (List blood transfusions, needle stick injuries, IV drug use, STDs, partners who may have placed you at risk, exchanging money for sexual activity, use of alcohol or drugs in association with sexual activity)
- Have you ever had any sexually related diseases?
- What do you do to protect your partner from contracting HIV?
- Do you or your partner use condoms? Always? Sometimes? or Never?

Historic Change for Sexual Health: High Impact Prevention (HIP)

The recent CDC approval of the use of an ARV, Truvada, taken daily as an HIV prevention strategy is historic (CDC 2014). Some suggest that there are parallels to the introduction of “the pill”. Providers must familiarize themselves as must their patients with this prevention option now approved. Its impact on the sexual health of older adults with and without HIV infection may well be immense and signal the beginning of the end of AIDS (CDC, 2014).

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Osteoporotic bone disease affects persons with HIV infection disproportionately when compared to others of similar age. Bone density is lower, and the fracture rate as much as 60% higher, in HIV-infected individuals (Arnsten et al. 2007; Triant et al. 2008; Womack et al. 2011). This may be explained by conventional risk factors that are more common among those with HIV, such as low body weight, cigarette smoking, alcoholism, hypogonadism, opiate use, and vitamin D deficiency. However, the proinflammatory state of HIV infection and direct viral effects on bone formation and resorption likely play a role as well (Walker Harris et al. 2012).

HIV/AIDS has been added to the most recent iteration of the National Osteoporosis Foundation (NOF) Guidelines as a risk factor for osteoporosis (2013). Additionally, studies have demonstrated a high rate of secondary causes of osteoporosis in individuals with HIV (Walker Harris et al. 2012). HIV/AIDS has been added to the most recent iteration of the National Osteoporosis Foundation (NOF) Guidelines as a risk factor for osteoporosis (2013). Additionally, studies have demonstrated a high rate of secondary causes of osteoporosis in individuals with HIV (Walker Harris et al. 2012).

In regards to screening for abnormal bone mineral density, the 2013 Primary Care Guidelines for the Management of Persons Infected with HIV recommend dual-X-ray absorptiometry (DXA) scan for all HIV-infected women who are postmenopausal and all HIV-infected men over the age of 50 (Aberg et al. 2014), though the cost-effectiveness of this strategy has not been well defined. Screening should be considered for all HIV-infected individuals who fall into these risk groups and should be prioritized for those with additional risk factors, such as those listed above. An evaluation for secondary causes of osteoporosis is also important, including a screen for vitamin D deficiency.

Treatment strategies for osteoporosis in HIV-infected persons are similar to those for HIV-uninfected persons. Good bone health depends first and foremost on good nutrition, with adequate intake of calcium and vitamin D, as well as avoidance of serious systemic illness, smoking and alcohol (McComsey et al. 2010; Qaseem et al. 2008). Patients should receive nutritional counseling if osteoporotic, and vitamin D supplementation if deficient. Weight bearing and strengthening exercise should be advised. Attempts to modify known risk factors should be encouraged. Osteoporosis should be treated aggressively with conventional modalities appropriate to the individual patient and as outlined by national guidelines (AHRQ Guideline Summary 2007; Qaseem et al. 2008; NOF Guidelines 2013). Androgen supplementation should be an individual decision between patient and provider and was not deliberated by the Panel. Similarly, decisions for changing antiretroviral therapy due to decreased...
bone mineral density should be individualized.

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Introduction: The use of ART therapy in HIV-infected individuals has substantially reduced morbidity and mortality from HIV-related causes; however, as life expectancy has improved, complex interactions between aging-associated and other comorbidities complicate medical management and limit survival in these individuals. Many of these factors affect the kidney; thus, acute and chronic kidney diseases account for significant morbidity and mortality in 30% of HIV-infected individuals (Adih, 2011).

New approaches to estimating glomerular filtration rate (eGFR): In order to accurately identify individuals with kidney disease and to make appropriate adjustments in drug dosing, ongoing efforts seek to identify the best, clinically available means of accurately estimating GFR. Initial studies using cystatin C measurements appeared promising; however, recognition of limitations prompted evaluation of combinations of creatinine- and cystatin C-based equations ((Aras, 2012; Liu, 2013; Steffl, 2012). Despite these efforts, considerable variability in results persists. These have been attributed to small numbers of subjects, the possibility that different methods perform differently in sub-populations of subjects, and the lack of correlation with clinical outcomes (Steffl, 2012). Although the use of very accurate estimates of GFR within and across study populations is essential for establishing outcomes in clinical trials; when using the same method over time, existing methods are reliable in assessing stability or change of kidney function in individual persons. Furthermore, they provide general guidance in staging chronic kidney disease (CKD). In the care of individual patients, a change in kidney function should always prompt an evaluation of potential causes, and appropriate interventions to protect kidney function. With regard to adjustment of drug dosing, two studies in older individuals or HIV-infected persons concluded that creatinine-based methods (Cockcroft-Gault equation or Modified Diet in Renal Disease (MDRD) formulae) performed best (Dowling, 2013; Vrouenraets, 2012).

*The Kidney in HIV and Aging*

- Identify and treat newly identified causes of changes in kidney function.
- Kidney function should be monitored at least annually using serum creatinine and other clinically available estimates of GFR.
- Urinary albumin excretion should be measured at least annually.
- Individuals with eGFR < 60ml/min (defined as CKD, NKF State 3) should have a nephrologist involved in the patient care team.
- Individuals with known CKD should be referred for planning for kidney replacement therapy when eGFR <15 ml/min.
- In order to minimize risk of developing acute kidney injury, careful monitoring and adjustment of drug dosing, particularly tenofovir, should be perform.
Aging nephropathy and HIV infection: Recent data from biopsies of older individuals without clinical evidence of kidney disease show significant structural abnormalities, including glomerular and tubulointerstitial fibrosis, which correlate with advancing age (Rule, 2010; Tan, 2010). In the absence of other diseases (e.g. hypertension, diabetes, HIVAN, etc) (Medapalli, 2012), and in the absence of albuminuria, cross-sectional studies suggested that aging nephropathy per se may not directly affect mortality; however, longitudinal studies in older individuals show progression of CKD and the development of complications with time (Giannelli, 2011; McIntyre, 2011). Recent studies continue to emphasize that aging nephropathy increases the risk for development of acute kidney injury, followed by rapid progression to ESKD, even in individuals who initially recover from acute kidney failure (Del Giudice, 2012). As existing kidney disease is associated with faster progression to AIDS and death, older individuals with aging nephropathy who become infected with HIV would be at increased risk for AIDS progression.

Several anti-retroviral therapies have been associated with changes in kidney function, nephrolithiasis (atazanavir), rhabdomyolysis, and acute kidney injury. Individuals with underlying aging nephropathy will be at increased risk for development of drug-related toxicities. Proximal tubulopathy (Fanconi syndrome), characterized by tubular proteinuria, glycosuria, hypophosphatemia, hypouricemia, hypokalemia and renal tubular acidosis, is a recognized form of tenofovir toxicity. Individuals with aging nephropathy also have abnormal tubular function (Sands, 2012), which may aggravate drug toxicity and make identification of etiology difficult. Although careful adjustment of drug dosing with tenofovir has reduced the risk for acute effects on kidney function, long-term studies have established increased risk for development of CKD in tenofovir-treated patients (Monteagudo-Chu, 2012).

Chronic kidney disease (CKD) in persons with HIV: The use of ART has substantially reduced viral load in HIV-infected individuals, and with it, kidney infection with HIV and the consequent development of HIV-associated nephropathy (HIVAN). Yet, among HIV-infected individuals with CKD, up to 60% will have evidence of collapsing glomerulopathy (HIVN) on biopsy, therefore representing a significant cause of CKD in this population (Ando, 2012; Scarpino, 2013). Also, despite advances in HIV treatment, co-infection with hepatitis C, hypertension, diabetes, nephrotoxicity from medications, age, male gender, and the use of tenofovir or ritonavir-boosted protease inhibitors contribute to the 30% prevalence of advanced CKD in HIV-infected individuals. As individuals with HIV age and older individuals become infected with HIV, appropriate diagnosis and management of these risk factors are important in preserving kidney function. In 2013, the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (KDIGO, 2013)) reported on the risk for CKD progression that incorporates cause of CKD, GFR category, and albuminuria category, where CKD is defined as abnormal kidney structure or function that is present for more than 3 months. For any given level of GFR, the greater the degree of albuminuria, the higher the risk for progression, including in HIV-infected individuals (Yanagisawa, 2013). Based on these criteria, in addition to eGFR, it is essential to measure urinary albumin excretion (mg albumin/mg creatinine) to assess risk. Current guidelines suggest involvement of a nephrologist in the care of
all individuals with identified CKD. Prevention of progression of disease is an important goal, prior to the time when referral for evaluation for dialysis and transplantation are required.

Kidney transplantation in HIV infected individuals: In the era of improved survival with ART treatment of HIV+ individuals with ESKD, kidney transplantation has become feasible. Similarly, increasing numbers of older individuals have also achieved satisfactory outcomes with organ transplantation. Yet, in both groups, recent studies have shown reduced graft function as compared to HIV-negative and younger individuals. Canaud et al (2013) showed that despite lack of detectable HIV in blood, the kidney allograft is infected with HIV in 68% of biopsies, and a significant number will develop clinical evidence of HIVAN in the transplanted kidney. Kidney infection correlated with and could potentially be diagnosed by detection of HIV DNA in the urine. At the end of 1 year nearly half of transplant recipients will have had episodes of acute rejection, a rate double that of HIV-negative individuals (Locke, 2013). Fressetto et al (2013) and Harbell et al (2013) have examined the drug-drug interactions among allograft immunosuppressive agents and ART, showing a variety of complex interactions that require frequent monitoring of drug levels to avoid drug toxicities or inadequate immunosuppression. Evidence that individuals with clinically diagnosed acute rejection also have kidney infection with HIV, further complicates selection of appropriate therapy in the face of a change in kidney function (Canaud, 2013). This complexity identifies the ongoing challenge of managing HIV-infected individuals with ESKD.

References


Excellent review of kidney disease in association with HIV infection.


As reviewed in the original monograph, a growing body of evidence indicated that older persons with hypertension benefit from treatment, but, suggested that the therapeutic target should be a systolic pressure below 150, in contrast to the recommendation that systolic pressure be reduced below 140 in younger persons. In large part this difference in recommendation grew out of the recognition that older persons were more susceptible to orthostatic hypotension, changes in kidney function, and other side effects when attempts were made to adjust drug doses to achieve target goals. The recently released guidelines for the management of hypertension in adults (JNC8) (James et al, 2013) confirms this recommendation in individuals over the age of 60. However, for all age groups with diabetes or non-diabetic kidney disease, BP goals should be below 140/90. There are no specific studies that address treatment guidelines for individuals with HIV or older individuals with HIV; however, given the complex co-morbidity (diabetes, chronic kidney disease) that often exists in this population, the recommended target goal will likely be below 140/90. Recommendations regarding the use of specific agents are unchanged, and the details are outlined in the JNC8 guidelines (James et al, 2013). As noted by the JNC8 report, guidelines are not a substitute for careful clinical judgment, particularly in complex patients with competing risks. Target goals may not be achieved in individuals that develop complications of treatment.

As discussed above, the presence of CKD in individuals with hypertension poses additional challenges in management, and has important implications for progression of CKD. Evidence that the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers provide renoprotective benefits beyond lowering of blood pressure, supports arguments that they be considered as first line choices in the treatment of hypertension in HIV-infected individuals with CKD. As discussed in the original monograph, the use of these agents may also be effective in older individuals traditionally thought to have low renin states.

Sympathetic innervation of the kidneys plays a major role in the pathogenesis of hypertension through modulation of glomerular filtration rate, sodium handling, and renin secretion. Clinical trials are currently being conducted in which bilateral, afferent and efferent renal nerves are ablated using radiofrequency-based systems. The initial results of safety, efficacy, and duration of response are promising. All studies have been limited to

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**Hypertension in HIV and Aging**

- Target BP for older patients with HIV and co-morbidities should be below 140/90
- Target systolic blood pressure should be below 150 mm Hg in patients susceptible to hypotension
- Treatment of hypertension should generally follow JNC 8 guidelines
- In patients with CKD, HIV and hypertension, use of an angiotensin converting enzyme inhibitor should be first-line treatment for hypertension

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individuals in whom secondary causes of hypertension have been excluded, and who fail to respond to standard therapeutic approaches. Limited data suggest that end-organ damage from hypertension may be arrested or improve after renal nerve ablation. No current studies have addressed the particular role in older individuals or those with HIV; yet, physicians caring for complex, and sometimes difficult to manage patients should be aware of emerging technologies. Several consensus reports about renal nerve ablation have been recently published (Gulati, 2013; Palmer, 2013; Schlaich, 2013; Thorp, 2013).

References


Screening for cognitive impairment is important. A two-tiered approach assessing symptoms with follow-up testing is a reasonable paradigm to follow for busy practices. Cognitive disorder remains a frequent problem despite effective antiretroviral therapy. Up to 50% of HIV patients will perform in an impaired range on neuropsychological testing batteries; however, only about a quarter of these patients will endorse symptoms and less than half of those are estimated to have HIV-associated dementia (HAD) (Heaton et al. 2010). Patients at particular risk are those with previous CNS disease, a low nadir of the CD4 cell count, detectable plasma viral load, and a low current CD4 cell count (Heaton et al. 2010; Cysique et al. 2010). Co-existing morbidities contribute to poor neuropsychological performance. These include diabetes, hypertension, HCV co-infection, medication toxicities, and psychoactive substance use disorders (Goodkin 2009). Among older HIV infected individuals, one must also consider concurrent neurodegenerative disorders, principally Alzheimer’s disease, and the cognitive impact of cerebrovascular disease (Valcour et al. 2004). The demonstrated disease heterogeneity and the relatively high frequency of asymptomatic cognitive impairment must inform screening approaches for them to be effective, and the selection of optimal screening instruments remains an issue in the field to date (Goodkin et al. in press).

The diagnosis of HAD for research studies now requires: (a) acquired moderate-to-severe neuropsychological testing impairment, documented by a score at least 2 SDs below demographically corrected normative means in at least 2 different cognitive domains, (b) moderate-to-severe difficulty in functional status in activities of daily living due specifically to this impairment, (c) a duration of at least one month, (d) absence of delirium and (e) absence of confounding conditions capable of otherwise explaining the impairment (Antinori et al. 2007). Mild Neurocognitive Disorder (MND) is defined by the following features: (a) an acquired mild level of neuropsychological testing impairment documented by a score of at least 1 SD below demographically-corrected norms on tests in at least 2 different cognitive domains, (b) the impairment interferes at a mild level with functional status, and (c) through (e) -- as above for HAD. Finally, the impairment cannot occur solely as part of a delirium and, as in the American Academy of Neurology-defined criteria, the diagnosis is possible only if the impairment cannot be explained by comorbid conditions. Asymptomatic Neurocognitive Impairment (ANI) requires the same level of cognitive impairment as MND, but without any functional status deficit. The differential diagnosis of these

*Older Age and HIV-Associated Neurocognitive Disorder (HAND)*

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diagnostic entities cannot be determined by screening instruments but require more in-depth neuropsychological testing. Brief clinical screening techniques can and should be employed before more formal and comprehensive NP testing is sought. Overall, for HAD, it appears that there is consistent evidence for aging as a risk factor (Janssen et al. 1992; McArthur et al. 1993; Chiesi et al. 1996; Valcour et al. 2004). This association of aging with HAND appears to be dependent upon the level of severity of HAND – greatest with HAD, less prominent with MND (formerly minor cognitive-motor disorder) (Goodkin et al. 2001; Larussa et al. 2006; Wilkie et al. 2003; Cherner et al. 2004) and least consistent with overall cognitive impairment (Hardy et al. 1999; Hinkin et al. 2001; Wilkie et al. 2003; Cherner et al. 2004).

**Cognitive Screening and HAND**

The high frequency of impairment and the knowledge that poor neuropsychological testing performance correlates to impaired performance on functional status tests and adherence to antiretroviral medications confirms cognitive screening to be clinically important. Quick and simple screening instruments exist for the most severe form of HAND (which is HAD) and Alzheimer’s disease (AD) and vascular cognitive impairment. However, the overlap in content of these tests is necessarily limited given the differing presentations, particularly for AD (cortical impairment) versus HAND (sub-cortical impairment). Thus, optimal screening strategies for older HIV infected adults need to cover broader areas than individual screens allow. Unfortunately, The tests designed to identify HAD perform considerably less well for milder conditions (MND and ANI) and cannot be recommended for this purpose. and may need to be supplemented by other tests (such as the Trail Making Test) for this purpose (Chalermchai et al., 2013; Goodkin et al., in press).

Regarding the available screening tests, the Montreal Cognitive Assessment (MOCA) Test might be suggested to best match the requirements for a screening instrument in an older HIV infected population. This is because it taps areas of cognitive performance involving executive functioning and other higher cognitive abilities thought to be most vulnerable in milder HIV-associated impairment, while remaining broad enough to detect diseases such as AD. However, validation studies are lacking, and early findings suggest that this test may have sizable limitations; some of which may be improved by augmentation with other tests, particularly those of information processing speed. The HIV Dementia Scale (HDS) is a well established test in HIV infection with a psychometrically sound introductory validation study from the pre-HAART era; however most studies in the current era demonstrate that it fails to identify all but the more severe forms of impairment. The International HIV Dementia Scale (IHDS) is useful within the USA for patients from other cultures, of which Hispanics would be the most numerous, but maintains similar limitations as does the HDS (Sacktor et al. 2005) (Bottiggi et al. 2007; Richardson et al. 2005; Smith et al. 2003; Morgan et al. 2008; Davis et al. 2002). Since the Mini Mental State Examination does not tap domains that are typically impaired in HAND and since there are data demonstrating its lack of efficacy, it should not be used for screening in this setting.

Currently, consensus recommendations on the treatment of HAND are concordant in a focus on the use of a stable, effective ART regimen. Beyond
this, the American Psychiatric Association Practice Guidelines for HIV/AIDS (Folstein et al. 2006; OARAC DHHS Panel Working Group of the Office of AIDS Research 2011) (McDaniel et al. 2000; Forstein et al. 2006) and the Guide for HIV/AIDS Clinical Care (DHHS, 2011) recommend the use of CNS-penetrating antiretroviral therapy regimens and the psychostimulants. However, it should be noted that there is considerable variability in how this approach is applied since there are no large-scale intervention trials that have consistently demonstrated efficacy for these recommendations and since a randomized controlled study designed to investigate a CNS-penetration effectiveness intensification approach failed to show benefit and actually identified worse performance in the CNS intensified (Marra et al. 2009). Yet, these results should be related to the limitations of using a measure of penetration rather than achieving the IC95 for that specific ARV in the CSF and to the limitations of the CSF as a window into the processes occurring in brain tissue.

These approaches need to be considered in the context of medication side-effect, antiretroviral adherence and the risk of exposure to new medications that could alter resistance profiles and long-term HIV outcomes. More research is needed. An exclusionary work-up for non-HIV-associated treatable causes of neurocognitive disorder, such as thyroid disease, syphilis, and B12 deficiency as well as conditions specific to HIV infection is important. Patients with presentations suggestive of CNS opportunistic infection or tumor, such as focal neurological findings, require careful evaluation, as do cases with more rapid neurological progression. Use of medications with higher CNS penetration effectiveness have clearly demonstrated utility in these focused situations, particularly in rare cases of CNS escape where virus is identified in CSF despite suppression in plasma. In addition, the psychostimulants have some evidence for efficacy in smaller studies (Fernandez et al. 1988; Van Dyck et al. 1997; Hinkin et al. 2001) Other therapies that may have promise for research studies include the use of anti-inflammatory agents, neurotrophic factors, nutritional supplements, and antioxidants, although a recent trial using minocycline as a novel antioxidant did not demonstrate efficacy. More research is clearly needed. Based on general recommendations applied to HIV-negative populations, exercise [both physical (Fazeli, et al., 2014) and mental], remaining socially engaged, monitoring for depression, and monitoring for cerebrovascular risk factors are relatively safe and possibly effective adjunctive strategies.

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HIV-1-associated peripheral neuropathy is currently the most common neuro-AIDS condition. Distal sensory polyneuropathy (DSP) is the most common type of peripheral neuropathy in the HIV infected. Others include progressive polyradiculopathy (most commonly occurs with advanced immunosuppression and usually caused by CMV), mononeuropathy multiplex that occurs in early HIV infection), autonomic neuropathy (which may be caused by central or peripheral nervous system abnormalities), and diffuse infiltrative lymphocytosis syndrome. With regard to DSP, one type of DSP is due to HIV infection itself, and another type is due to antiretroviral (ARV) toxicity, predominantly from the dideoxynucleosides (didanosine and stavudine). Mechanisms of disease are incompletely understood, with some evidence implicating gp120-mediated neuronal apoptosis for viral-induced DSP and mitochondrial toxicity with or without DNA polymerase \( \gamma \) involvement in dideoxynucleoside toxicity-induced DSP (Ng et al., 2011). However, data have implicated the protease inhibitors as well in toxicity-induced DSP (Lichtenstein et al. 2005), and protease inhibitor exposure has been noted as an unrecognized risk factor for the development of DSP (Pettersen et al., 2006). In addition, dapsone, isoniazid, metronidazole, vincristine, thalidomide, and hydroxyurea all appear to increase the risk of DSP. Patients report pain, numbness, and dysesthesias occurring first in the feet and gradually ascending — though infrequently to the level of the finger tips. Motor symptoms are minimal. The symptoms typically show a limited response to treatment. HIV-associated DSP occurs more frequently in older patients (Chen et al., 2013). However, DSP is not as clearly shown to be related to markers of HIV disease progression — as was the case in the era prior to effective ART. While there is a current association with age, diagnosis of AIDS, and exposure to neurotoxic ARVs, there is not one with clinical HIV disease stage, time from diagnosis, current CD4 cell count (across the entire range), or plasma viral load. Aging is independently associated with deterioration of light touch in both the soft and callous skin of the foot (Mitchell and Mitchell, 2000). DSP causes significant, ongoing pain, is associated with decreased ARV adherence (threatening control of systemic HIV disease), and has been demonstrated to be a true risk factor for falls in older people (Munhoz et al. 1995). It has also been associated with the comorbidity of HIV-associated neurocognitive impairment. Isolating the source of neuropathic pain is a particular concern in the older HIV infected patient, who may be suffering from several conditions causing pain and may not be able to distinguish the specific component of neuropathic pain well. In fact, the prevalence of pain amongst HIV-infected patients generally had been reported to range from a point prevalence of 54% to 83% over a three-month recall period, with moderate-to-severe intensity in one to two and a half different anatomical sites (Parker et al., 2014). Older patients diagnosed with DSP should have their pain assessed with standardized pain scales and should receive specific attention to ARV toxicity, maximal pain control, and regular reviews of ARV adherence. A number of comorbidities may
increase the likelihood of HIV-associated DSP. Diabetes is capable of substantially raising the risk for DSP. This is a significant clinical concern, given the impact of ARV toxicity-associated insulin resistance and diabetes in the setting of HIV infection. Moreover, ongoing studies have shown an association between high triglyceride levels and DSP. In addition, patients with HCV co-infection are at risk for DSP, though this comorbidity is more likely in the younger age range. Treatment is of two types, causal and symptomatic. Regarding causal treatment, avoiding neurotoxic medications, correcting vitamin B6, B12 and folate deficiencies, and considering thiamine replacement are important, if the patient is malnourished. It should also be noted that overdosing with B6 supplementation can cause a peripheral neuropathy. It should also be noted that the use of statin drugs has been associated with significantly lower odds of a DSP diagnosis (Chen et al. 2013). Regarding symptomatic treatment, it is useful to consider non-pharmacological treatments to reduce pain, e.g., advising patients to avoid extended periods of standing or walking, to wear looser shoes, to soak their feet in ice water, to take safety precautions to reduce fall risk by compensating for sensory loss. Therapeutic shoes may also be prescribed. Regarding medications, the antidepressants have been used frequently, particularly low doses of amitriptyline. However, the antidepressants as a class have not always been shown to have specific analgesic efficacy for DSP in trials that were considered to be well controlled (Goodkin et al. 1989, 1996;1998). While amitriptyline has been suggested to be equivalent to nortriptyline in efficacy for neuropathic pain (Liu et al., 2014), amtriptyline was specifically not shown to be more effective than placebo in ACTG 242 for HIV-associated DSP (Kieburtz et al. 1998)—suggesting that nortriptyline may be preferred in the setting of HIV infection. Some credence has been given to the notion that the specific sub-group of serotonergic and noradrenergic reuptake inhibitor (SNRI) antidepressants (such as venlafaxine and duloxetine) might be more efficacious for pain; however, this cannot be considered to be empirically confirmed. The anticonvulsants have also been used, with gabapentin as well as pregabalin being touted for efficacy. A randomized, double-blind, placebo-controlled trial of pregabalin failed to demonstrate significant improvement of pain, but hyperalgesia was less pronounced in participants receiving pregabalin compared to placebo (Simpson et al., 2010). Carbamazepine has been used as well but represents a concern regarding drug-drug interactions. Regarding other drugs for symptomatic treatment, some controlled evidence does show a therapeutic effect of lamotrigine in a small trial (Simpson et al., 1998) followed by a subsequent larger study (Simpson et al. 2003); however, a meta-analysis reported that lamotrigine was not more effective than placebo. Lidocaine gel (5%) initially showed promise in an open label study but failed in a controlled clinical trial (Estanislao et al. 2004). A high-dose capsaicin patch has shown controlled evidence for its use in a sample of good size (Simpson et al. 2008). A trial of the neurotrophic factor, prosaptide, was terminated on the basis of a planned futility analysis (Evans et al., 2007). Acetyl-L-carnitine was unsuccessful as a booster of mitochondrial function in treating HIV-associated DSP in a small open-label study of 20 patients (Osio et al, 2006) and in a randomized, placebo-controlled trial of 90 patients (Youle et al., 2007). Although nerve growth factor (NGF) did show improvement of symptoms of HIV-associated DSP in an open-label study of 200 patients (Schifitto et al., 2001) and a randomized placebo-
controlled trial of 270 patients (McArthur et al., 2000), it was associated with significant injection site reactions and is not currently available for clinical use. Memantine (Schifitto et al., 2006), mexilitine, and peptide T (Simpson et al., 1996) have been studied with no apparent effect. More recently, the CCR5 antagonist, vicriviroc, was not found to improve pain in a placebo-controlled trial of 118 patients with HIV-associated DSP (Yeh et al., 2010). Thus, use of the foregoing medications frequently does not achieve a level of pain control that satisfies the patient, and treatment with opioid analgesics (e.g., tramadol, morphine, oxycodone, methadone) can and should be undertaken, as necessary, to maximize pain control and optimize ARV adherence and activities of daily living while minimizing side effects in all patients at need (including those with a history but no current evidence for substance dependence). Use of the WHO Ladder is a generally acknowledged approach, which can be effectively supplemented by formal pain contracting and monitoring of efficacy with brief, standardized pain scales (such as the Visual Analogue Scale) and of abuse and diversion with urine toxicology screens.

References:


Before the advent of potent antiretroviral therapy, the autonomy and rights of people with AIDS was a common theme of discussion among patient advocacy groups and care managers (Mor et al. 1989). When HIV infection was more acutely life-threatening, it was incumbent upon everyone involved in the care of these individuals to ensure that they had considered advance care planning and surrogate decision-making as a routine part of care. Early in the epidemic it was common for HIV-infected patients to have a durable power of attorney (DPOA) for healthcare and an advance directive or living will (Steinbrook et al. 1986). Since the arrival of potent combination ART, this practice has declined substantially as persons with HIV infection have led healthier, longer lives (Selwyn et al. 2003). Recent data show that less than half of HIV-infected patients age 45-65 have completed advance care planning and advanced care planning discussions between patient and provider are less likely amongst certain patient groups, such as ethnic minorities, intravenous drug users, and those with lower education levels (Erlandson et al. 2012, Wenger et al. 2001).

For persons with advancing age and longstanding HIV infection, particularly those with even modest cognitive or functional impairment or with multiple comorbidities, it seems wise to re-emphasize the importance of establishment of power of attorney and advance directives, since, as it was 20 years ago, many persons with HIV infection may not want their closest blood relative or other default surrogate decision maker (based on state law) to make medical decisions for them in the event of serious illness. While rates of opportunistic infections and AIDS-related malignancies have decreased, many individuals with HIV suffer from multiple, complex chronic conditions, making end-of-life discussions as valuable as ever. The increased longevity of persons living with HIV leads to increased opportunities for advanced care planning and providers should incorporate such discussions into routine care for these individuals (Selwyn et al. 2003).

Additionally, over the past 2 decades, confidence in the effectiveness of established advance directives has grown. Research during the 1990's led to some discouragement about the effectiveness of advance directives in guiding care decisions (SUPPORT) (Teno et al. 1997). More recent evidence, using agreed upon directives established between providers and patients or their surrogates, such as the “Physician Orders for Life Sustaining Treatment” or POLST form (2010), have indicated that patients and providers may be able to have more confidence that directives
will actually be followed as patients move from home to various care settings (Hickman et al. 2010).

References


*Depression in HIV and Aging*

- Older HIV infected patients should be screened for depressive disorder with an appropriate standardized measure (such as the Geriatric Depression Scale) that minimizes the impact of somatic depressive symptoms.

Disorders associated with depressed mood have been estimated to occur in a majority of HIV infected patients over the course of infection. Depressive spectrum disorders frequently occur at the point that an HIV infected patient is confronted by greater HIV symptom burden (Atkinson et al. 2008; Sherr et al. 2008). The depressive disorders run the gamut from adjustment disorder to dysthymic disorder to major depressive disorder and bipolar affective disorder (with depressive episodes) with and without psychotic features. Data from the Veterans Aging Cohort 5-Site Study demonstrated that depression rates increased with age (Justice et al. 2004), although this is not without exceptions (Karl Goodkin et al. 2003; Rabkin et al. 2004). Social support is a critically important cofactor in examining a depression diathesis in the older HIV infected persons (Shippy & Karpia 2005; Shippy & Karpia 2005), as are stressful life event burden (Wight et al., 2012) and coping strategy (Rodkjaaer et al, 2013). Newly infected older HIV adults, in particular, may be isolated from supportive networks due to the stigma of HIV/AIDS and due to ageism and may suffer from higher incidence of depression. Untreated depression is a predictor of non-adherence to medication regimens, which in turn has an adverse effect on overall morbidity and mortality (Gonzalez et al. 2011; Wada et al., 2013). The elevated physical symptom burden associated with depressive disorders and suicide risk may be further enhanced by concurrent psychoactive substance use and an elevated pain level (Tsao et al. 2005) as well as by other psychiatric disorders generally. A study of persons triply diagnosed with psychiatric disorders, substance use disorders, and HIV/AIDS demonstrated high rates of depressive symptoms and showed that 72.9% of participants met criteria for major depressive disorder (Berger-Greenstein et al. 2007). Older patients may be yet at greater risk. One must screen out other causes of depressive symptoms presenting in HIV infected patients, including HIV wasting syndrome and early HIV associated depression (HAD) as well as iatrogenic causes (e.g., interferon-alpha toxicity in the treatment of HCV co-infection). However, in the case of HAD (and HAND more generally) major depressive disorder might be more importantly considered as a co-morbid disease. In fact, recent research in major depressive disorder suggests that it is a disorder with a neuroinflammatory profile of its own and increases pro-inflammatory cytokine production. Adding to this focus, one study has demonstrated that persistent, detectable CSF viral load was associated with increased risk of new-onset of major depressive episodes, extending the link from the inflammatory response to virologic suppression. Detectable CSF but not plasma viral load was associated with a 4.7-fold increase in new-onset depressive episodes, and depressive symptoms appeared to worsen over time in those with detectable CSF HIV RNA but improved over time in those with non-detectable CSF viral load.
Complementing these results, research outside of HIV infection has shown that major depression increases the likelihood that minor cognitive impairment will subsequently evolve into Alzheimer’s Disease. It might be anticipated that this would occur with yet greater probability in the setting of HIV infection, where the inflammatory response is already heightened on a chronic basis. Vitamin B12 deficiency has been associated with major depressive disorder in HIV infected patients (Baldewicz et al. 2000), and the treatment of vitamin B12 deficiency and possible vitamin B12 supplementation above normal levels may reduce risk of depressive spectrum disorders. Early HAD in an older patient typically presents with apathy, lethargy, and social withdrawal and may easily be confused with major depressive disorder (Goodkin 2009). It is important to note that major depressive disorder in older HIV infected patients may be treated with the same medications that would be indicated for younger patients. Side effect profiles and drug-drug interactions should be specifically considered in the choice of drug. Activating antidepressants with minimal effects on the CYP 450 isoenzyme system, such as venlafaxine, may be preferred. Of the selective serotonin reuptake inhibitors, paroxetine and citalopram would be preferred to fluoxetine.

References (Con’t in Anxiety Section)
Many anxiety disorders have not been studied as well as HAND or depressive spectrum disorders in HIV infection but would seem to be fourth in frequency amongst HIV infected patients—behind HAND, depressive spectrum disorders, and alcohol/substance use disorders and have been shown to be increased in likelihood with HIV infection (Lopes et al., 2012). Adjustment disorder is frequently noted after initial notification of HIV infected serostatus and may be the most common psychiatric disorder manifesting primarily with anxious mood. General medical causes of anxiety must be considered, including the early stages of pneumonia. Generalized anxiety disorder and panic disorder have been documented in 15.8% and 10.5% of HIV seropositive persons versus 2.1% and 2.5% of the general population, respectively (Bing 2001). Post-traumatic stress disorder has also been reported at a higher rate among the HIV infected (Israelski et al. 2007). This is particularly true for women, in whom a history of trauma could, in turn, relate to a decreased sense of empowerment and a decreased likelihood of negotiating HIV precautions with sexual partners. In a study examining age differences, the rate of anxiety disorders (panic disorder and generalized anxiety disorder) and PTSD were found to be somewhat more frequent in younger patients (at 22.5% and 16.1%) vs. older patients (at 17.7% and 6.6%, respectively (Zanjani et al. 2007). Anxiety symptoms have been specifically noted to threaten adherence measured by missed ARV doses, although older age was associated independently with a greater likelihood of maintaining the schedule of taking ARVs (Schönnesson et al. 2007).

In one recent study, 47% of patients demonstrated significant anxiety symptoms. Patients showing such anxiety symptoms had a high number of ARV switches (i.e., were at the fourth line or more) (Celesia et al, 2013). Psychopharmacotherapy for the anxiety disorders in HIV infected persons should be avoided whenever possible, particularly for older patients. Cognitive behavioral stress management, guided imagery, progressive muscular relaxation training, self-hypnosis, biofeedback, and other such behavioral techniques are preferred. However it may be useful to employ psychopharmacotherapy in low doses to support the older patient's sense of control and autonomy.

The most common anxiolytic therapies used— the benzodiazepines—are sedating, interact with alcohol, foster dependence, and are associated with drug
interactions on the cytochrome P450 (CYP450) 3A4 isoenzyme system (strongly inhibited by the protease inhibitors). If needed, on an ongoing basis, the SSRIs are generally preferred to the benzodiazepines. For short-term treatment, short- to intermediate-acting benzodiazepines with no active metabolites, such as lorazepam and oxazepam, may be employed. Buspirone is an option to consider that is non-sedating, safe in overdose, and has no abuse potential, although it does suffer from a delay in onset of action. Other options with no abuse potential include hydroxyzine, diphenhydramine, pregabalin and the nutritional supplement, valerian.

References
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Goodkin, Karl et al., 2003. Putting a Face " on HIV Infection / AIDS in Older Adults: A Psychosocial Context HEALTH NEEDS OF OLDER ADULTS LIVING. Group.
Older Age and Alcohol and Substance Use Disorders

Psychiatric disorders typically excluded in the literature on older HIV infected patients are alcohol and substance use disorders. However, illicit drug use has been reported by 45.1% of younger HIV infected patients and by 29.7% of older HIV infected patients — a non-significant difference (Zanjani et al. 2007). Most of the difference was due to increased cannabis use in younger patients. Non-cannabis drug use frequency was almost exactly the same in older and younger HIV infected patients. In a study of a cohort of veterans, those with current substance use disorder present who were over 50 years of age numbered 31% (Goulet et al., 2007). More research is clearly needed in the area of the impact of alcohol and substance use disorders in older HIV infected patients. Older Age and General Psychiatric Comorbidity Treatment of HIV infected patients with mental health and substance use disorders comorbidities results in the benefit of more consistent treatment of their HIV infection (Palepu et al. 2004; Sambamoorthi et al. 2000). Yet, it remains the case that little research targeting psychiatric comorbidities in older adults has been reported to date. It is important to note a caveat that the impact of mental health or substance abuse treatment alone on sexual and substance use risk behaviors may be limited, thus highlighting the importance of comprehensive care models that integrate behavioral health services with medical treatment of older HIV infected patients. Throughout this report substance use is cited as a key variable that must be considered in order to achieve optimal outcomes. It should be noted that an expanding number of pharmacotherapies that are either non-addictive or low in addictive potential have been reported to primarily affect substance use outcomes; these include bupropion, acamprosate, topiramate, buprenorphine, gabapentin, modafinil, armodafinil, flumazenil, naltrexone, and most recently naloxone administered by a new hand-held auto-injector to reverse opioid overdose. The co-occurrence of substance use with other mental health issues is clear, but it is also a significant factor in the comorbidities discussed in this report and their management. This challenge is reflected in the fact that almost any infectious disease occurs in the context of psychosocial factors such as unemployment, unstable housing, family problems and stigma.

References
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Summary and Conclusions

Throughout the consensus project, the Expert Panel and reviewers have been mindful of the high degree of variability of the health status of older persons with HIV/AIDS. Many of us care for HIV infected patients who are in their 70’s and are robust, have had an excellent response to HAART, and are living active and fruitful lives. Many are aging successfully. At the same time, we care for HIV infected patients in their 50’s with substantial cognitive and/or functional debility and multi-morbidity. We cannot emphasize enough that treatment strategies must be considered carefully and be individualized for that patient sitting before you, one at a time. This tenet has pervaded our judgment throughout this report.

The issues of multi-morbidity are critically important from the perspective of an individual patient. They become even more compelling from the broader view of providing care to populations of patients in the context of the present health system’s capacity. Reports (Yarnall et al. 2003; Østbye et al. 2005) illustrate that there is not enough time during the day for a family physician to carry out all recommended preventive processes for a representative panel of patients, let alone manage a typical panel’s burden of chronic disease.

What is needed are strategies to determine which elements of a treatment plan are most important, or have the highest priority (Justice 2006). Determining those priorities for an older adult with HIV must be based on the applicability of the evidence, the actual absolute risk reduction achieved in studies, the time needed to treat in order to observe the benefit, and the individual’s values and preferences. The patient’s values and preferences are critical on several counts: 1) what are the most important outcomes for them, 2) what are the burdens they are willing to endure in order to achieve those outcomes, 3) what are their preferences regarding the potential harms associated with the interventions, and 4) how does the level of uncertainty surrounding the reported benefits of a treatment affect their decision-making process.

A 2005 review of existing clinical practice guidelines for nine common chronic diseases demonstrated that the guidelines rarely consider co-morbid conditions for older patients. Criteria used in this review include consideration of issues pertinent to older adults or to people with co-morbidity: describing the target population for recommendations, reviewing the quality of evidence for older patients or patients with co-morbidity, addressing time needed to treat in order to observe benefit, the tradeoffs between short and long-term goals, treatment burden, and patient preferences (Boyd et al. 2005). Methods to tailor treatment and prevention strategies based on presence of multi-morbidity are emerging (Braithwaite et al. 2009; Braithwaite et al. 2007). Studies demonstrate that in some clinical situations, our ability to individualize medical decision making for older adults with differing patterns of co-
existing conditions is not easily achieved (Fraenkel & Fried 2010). As discussed in the Introduction, for older patients, there is increasing evidence that an array of symptoms or syndromes that are not defined as a disease per se, may be the best basis for the provider and patient to make decisions (Tinetti 2004).

Key concepts emerge from the literature on other co-morbid conditions that may have relevance to HIV. A framework for considering co-morbidity in patients with diabetes postulated that it may be worthwhile to determine whether there was a dominant condition (Kerr 2006). This dominance may arise from the condition being newly diagnosed, life threatening, and so serious that it eclipses the management of other conditions. In the absence of a dominant condition, it may be advisable to consider whether or not co-morbid conditions share an underlying pathophysiology and are likely to be part of a shared management plan (concordant) or not (discordant). Also, it may be relevant to the patient whether the co-morbid condition is symptomatic or asymptomatic. Finally, there is emerging literature that the treatment of some co-morbid conditions in an integrated manner may improve the outcomes for not only the targeted conditions but also other existing co-morbid conditions (Safren et al. 2009; Parsons et al. 2007). For example, the use of buprenorphine in primary care HIV clinics improves substance use outcomes and adherence to medical visits, which is associated with improved HIV outcomes (Lucas et al. 2010). Directly observed HAART in methadone clinics may also improve HIV outcomes (Lucas et al. 2006). For example, there is evidence suggesting that an integrated approach to diabetes and depression may improve outcomes for both; In HIV patients, better management of depression leads to better medication adherence for all existing comorbidities (Gonzalez et al. 2011). There is some evidence that an integrated approach with cognitive behavioral therapy can lead to improved adherence (Safren et al. 2009; Kinder et al. 2006).

Because new information is emerging rapidly in this fast-evolving field, the Expert Panel considered carefully how best to disseminate the information in this report. This project was conceived as an evolving effort that would require the addition of new information to improve its content and conclusions. Like cross-sectional data, typical publication “fixes” information in time and substance and does not lend itself well to this consensus project. Consequently, information will be updated at our Wikipedia-type web blog at http://www.aahivm.org/bulletin_pub/exec/default.aspx?pgID=MjIx&paID=Mw==www.

References


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Disclosures

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Appendix

What level of confidence do you have in this recommendation?

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Low – No or little evidence for this rec.
This rec. may seem very beneficial.
This rec. may be ineffective.
This rec. may be seriously undermined by research findings.
There may be a conflict.
This rec. may interfere with the goals of others.

Moderate – some evidence exists.
Moderate rec. seems promising.
Some evidence has been heard.
This rec. seems effective.
This rec. seems a valid threat.
I don’t anticipate that theory will interfere with the goals of others.

High – there is solid evidence that
very likely applies to older MCI.
This rec. is very unlikely to be harmful.
This rec. is very unlikely to be beneficial.
This rec. is very unlikely to interfere with the goals of others.

What priority would you give this recommendation?

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Low – not that important to implement.
(Not at all)
Others should take precedence.

Moderate – should be implemented.
Other rec. may take precedence.

High – this rec. should be implemented right away (as applicable).
