The HIV and Aging Consensus Project

Recommended Treatment Strategies for Clinicians Managing Older Patients with HIV

Sponsored by

American Academy of HIV Medicine

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Supporting Partner:

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THE HIV AND AGING CONSENSUS PROJECT:
RECOMMENDED TREATMENT STRATEGIES FOR CLINICIANS
MANAGING OLDER PATIENTS WITH HIV

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

Geriatric syndromes such as "frailty" and "disability" may require adaptation for those aging with HIV infection to account for the role of HANA in accelerated aging. The geriatric literature describes "frailty" as a pentad of loss of height, exhaustion, slowness, low physical activity and weakness (Desquilbet et al. 2007). According to a geriatric consensus conference, "frailty is evident over time through an excess vulnerability to stressors, with reduced ability to maintain or regain homeostasis after a destabilizing event" (Walston et al. 2006). Key to this concept is the sense of vulnerability to injury resulting from depleted physiologic reserve caused by multiple overlapping and interacting mechanisms. However, the geriatric research community continues to debate the best means of measuring vulnerability (Walston et al. 2006). A modified version of the frailty phenotype, the frailty related phenotype, has been applied among those with HIV infection with mixed success. While the measure demonstrated a stepwise association with increasing years on therapy when stratified by age at initiation, only 3.4% of HIV infected men 55 years or older demonstrated the phenotype (Desquilbet et al. 2007).

Functional capacity may be a more useful measure because functional capacity can be measured over a wider range of abilities (Gill 2002) and has demonstrated a greater applicability to HIV infected patients in care (Oursler et al. 2006). Indeed, initial work in the post HAART era suggests that functional limitation is at a much higher end of the spectrum than that seen among older, more typically considered a geriatric sample (Oursler et al. 2006; Oursler et al. 2009).

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). 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).

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). 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. Without such support they will be relegated at early ages to costly home health care services and long-term care facilities. 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).

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). 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 at. 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. 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)

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 multi-morbidity treatment regimen with the added implications of adherence as well as drug-drug, drug-disease and disease-drug interactions (Braithwaite et al. 2005). 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 highly active antiretroviral treatment (HAART) but how treatment of other conditions affects adherence to HAART, and adherence to the overall treatment regimen is not known.

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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Detection and Screening for HIV in Older Adults

- Providers must reduce barriers to effective prevention and detection of HIV in older adults. However, because providers and patients are unable to reliably estimate HIV risk in older patients, we suggest that primary care providers perform routine, opt-out HIV screening in *all* adults, regardless of age or individual factors, with repeat HIV screening at least annually in patients at known risk.

The number of older adults with HIV/AIDS is increasing, partly because people with HIV/AIDS are living longer. Currently, about 37% of all patients living with HIV/AIDS are older than 50, and by mid-decade this will increase to 50%. (CDC 2011). There has also been a continued lack of attention to the rate of new infections in older adults. Older adults account for 17% of newly diagnosed cases of HIV in the US and 24% of all new AIDS cases in 2009 (CDC 2011). One in 6 of all new HIV infections in the US occur in the older adult.

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). Injection drug use is less common, although it accounts for 16% of AIDS cases in older adults (CDC 2011) . Older women may be at increased risk of HIV due to age-related vaginal thinning and dryness (CDC 2008) 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 2008). Additionally, increasing prevalence of erectile dysfunction as men age may make condom use even more challenging. Minority races/ethnicities may also have increased risk factors (Zingmond et al. 2001). Older adults who are gay, bisexual or transgender (GBT) are an additional group at increased risk, especially men who have sex with men, who account for just over half of all new HIV infections. 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:* A study of older

women showed 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. Older adults are much less likely to use condoms than younger adults. For instance, a national survey of sexual practices found that older adults at risk of HIV infection were one sixth as likely as younger adults to use condoms during sex, and one fifth as likely to have been tested for HIV infection (Stall & Catania 1994).

2. *Underestimation of risk by healthcare providers*: 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 2008) .

3. *Misdiagnosis:* 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).

4. *Stigma:* HIV-infected older adults with HIV infection 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 2008) .

Communication between health care providers and patients is critical for HIV screening and detection. To reduce the risk of HIV transmission, providers must address the barriers to effective prevention and detection. 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. 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).

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). The CDC 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 (CDC 2008) (Henderson et al. 2004; Skiest & Keiser, 1997). Unfortunately, older patients also have little interest in HIV testing, even in the presence of risk factors (Akers et al, 2007; Lekas et al. 2005; Mack & Bland, 1999). Routine HIV screening in the general population is cost-effective even in health-care settings in which HIV prevalence is as low as 0.1% (Sanders et al. 2005). Analyses in older adults also 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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When to Initiate Antiretroviral Therapy in HIV and Aging

- Antiretroviral therapy should be initiated in all patients older than 50 who have a CD4 count less than 500 cells/mm^3
- Antiretroviral therapy should be initiated in all patients older than 50, regardless of CD4 cell count, with the following conditions: AIDS-defining illness, HIV-associated nephropathy, or chronic hepatitis B virus infection
- For patients over age 50 who have a CD4 count greater than 500 cells/mm^3, antiretroviral therapy should be considered. Factors favoring initiating therapy include plasma HIV RNA levels greater than 50,000 copies/ml, greater than 100-point decline in CD4 count in prior 12 months, or risk factors for cardiovascular disease.
- For patients who have diabetes or hyperinsulinemia (and no baseline antiretroviral drug resistance), an initial ritonavir-boosted protease inhibitor-based regimen should be avoided, if possible

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).

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.

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).

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 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). Antiretroviral 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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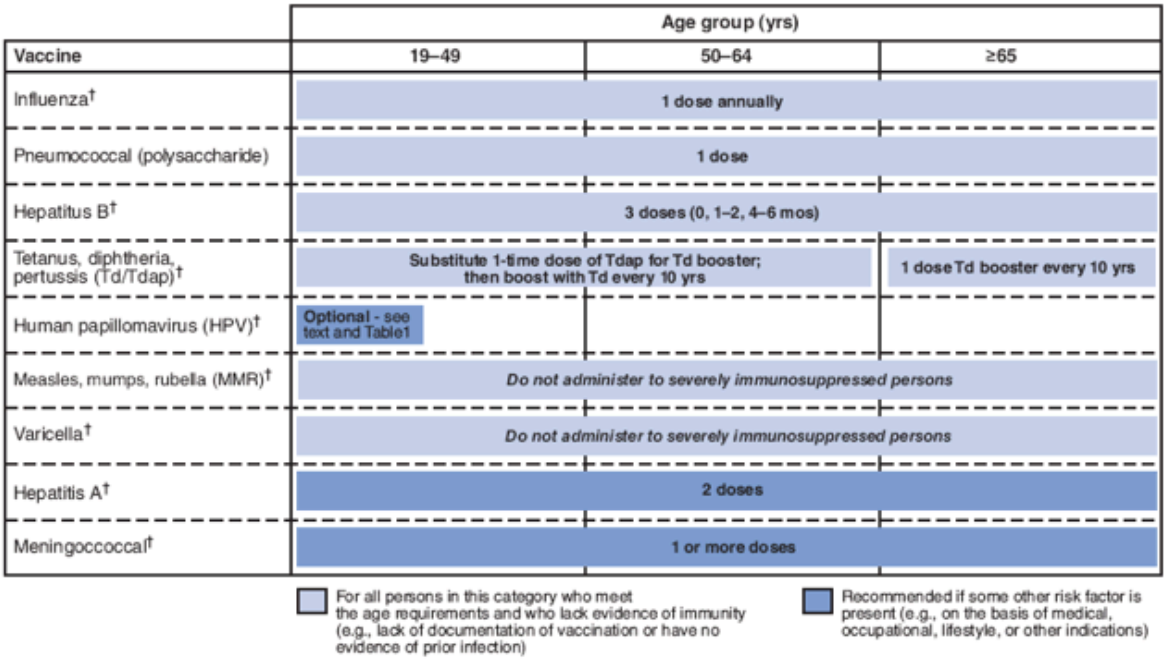
Immunizations in HIV and Aging

- 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 most some controversy exists with regard to pneumococcal vaccine booster strategies. Some authors suggest no booster, others a single booster at 5 years or once CD4 count increases to > 200/mm^3 if initially administered when the CD4 count was < 200/mm^3, and others a booster dose every 5 years (discussed in Rivas et al. (2007). Regular primary and booster dose schedules based on age for Td/Tdap, hepatitis A and B, and HPV are suggested in HIV patients. An aspects of vaccine administration though overall guiding principle is that live-attenuated organism vaccines are generally contraindicated, though when CD4 counts are > 200-400/mm^3 mumps, measles and rubella (MMR) and varicella vaccines are indicated in some patients.

Evidence for a change in vaccine responsiveness with advancing age in HIV subjects.

Vaccine responsiveness declines with age, but differs by the vaccine. For



* Adapted from the Advisory Committee on Immunization Practices (ACIP) Adult Immunization Schedule. For detailed information on immunization against influenza, pneumococcal disease, hepatitis B, human papillomavirus, varicella, and hepatitis A, see disease-specific sections in the text and in Table 1. For information on immunization against tetanus, diphtheria, pertussis, measles, mumps, rubella, and meningococcal disease, refer to recommendations of the ACIP (www.cdc.gov/vaccines/pubs/ACIP-list.htm).
† Covered by the Vaccine Injury Compensation Program.

Figure 1: From CDC website April 10, 2009 / 58(RR04); at **http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5804a1.htm**

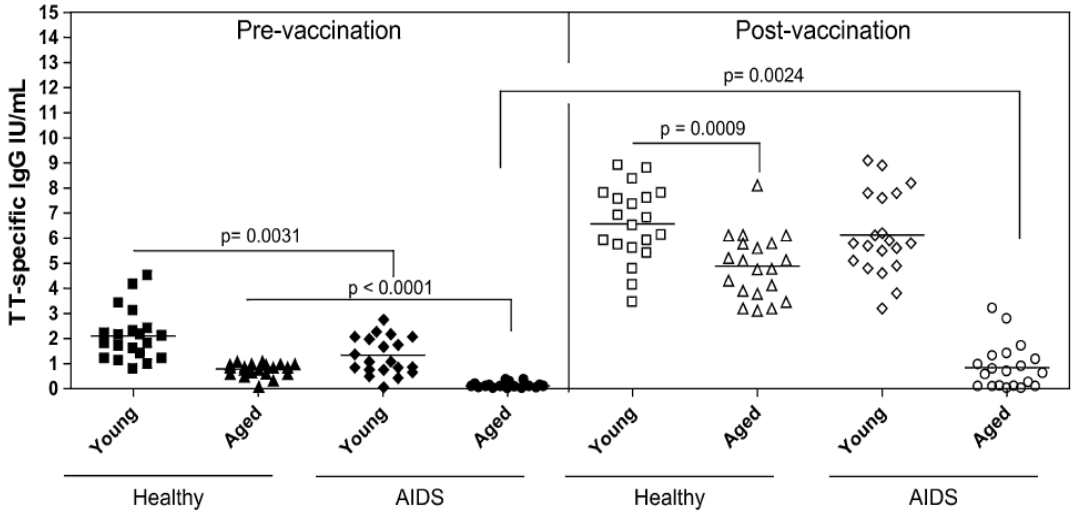


Figure 2 Failure of HAART in Reconstituting Immune Response to C. tetani Vaccine in Aged AIDS Patients. From Andrade R et al. *Failure of Highly Active Antiretroviral Therapy in Reconstituting Immune Response to Clostridium tetani Vaccine in Aged AIDS Patients.* JAIDS:54(1);10-17. Used by permission of the publisher

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 (High et al. 2010). 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. 2008) 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. 2008) 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 was estimated in a meta-analysis of 4 studies as 27-78% (Atashili et al. 2006). A randomized, controlled trial just prior to widespread HAART use demonstrated an efficacy of 41% (Tasker et al. 1999). No study has examined the effect of age in influenza vaccine efficacy in HIV-infected patients. Other data suggest vaccine failure occurs fairly regularly and most influenza-documented illness in HIV-infected patients represent vaccine failure (Tasker et al.1999). Finally, there is surprisingly little data on zoster vaccine in HIV-infected subjects despites 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 recently published (Andrade et al. 2010). 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 (Table 2) 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.

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Smoking Cessation in HIV and Aging

- Providers should counsel patients at every visit to stop smoking. Providers should make use of community smoking-cessation resources, online quit sites, and pharmacotherapy to assist patients in quitting tobacco use.

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. There has been a growing incidence of lung cancer among patients (Gritz et al. 2007) with HIV/AIDS. While about 20% of the general population in the US smokes, between 40% to 70% of HIV-infected people smoke (Crothers et al. 2005; Havlik et al. 2011). In the HAART-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. 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.

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Monitoring of Serum Lipids and Cardiovascular Disease Screening in HIV and Aging

- There is insufficient evidence to alter current recommendations for management of dyslipidemia or CVD/cerebrovascular disease screening by specific age criteria. It is reasonable to recommend Framingham Risk Score (FRS) assessment in addition to aggressive primary prevention using standardized guidelines for cholesterol and blood pressure (JNC-8). Whether or not screening for CVD/cerebrovascular disease and treatment of hyperlipidemia in the setting of HIV should be modified for age and/or for HIV itself remains unknown and will require further study.

A growing body of evidence suggests cardiovascular disease is more frequent in HIV-infected subjects (Klein et

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).

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

al. 2002; Triant et al. 2007). In one study, HIV-infected individuals presenting

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 1) 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:

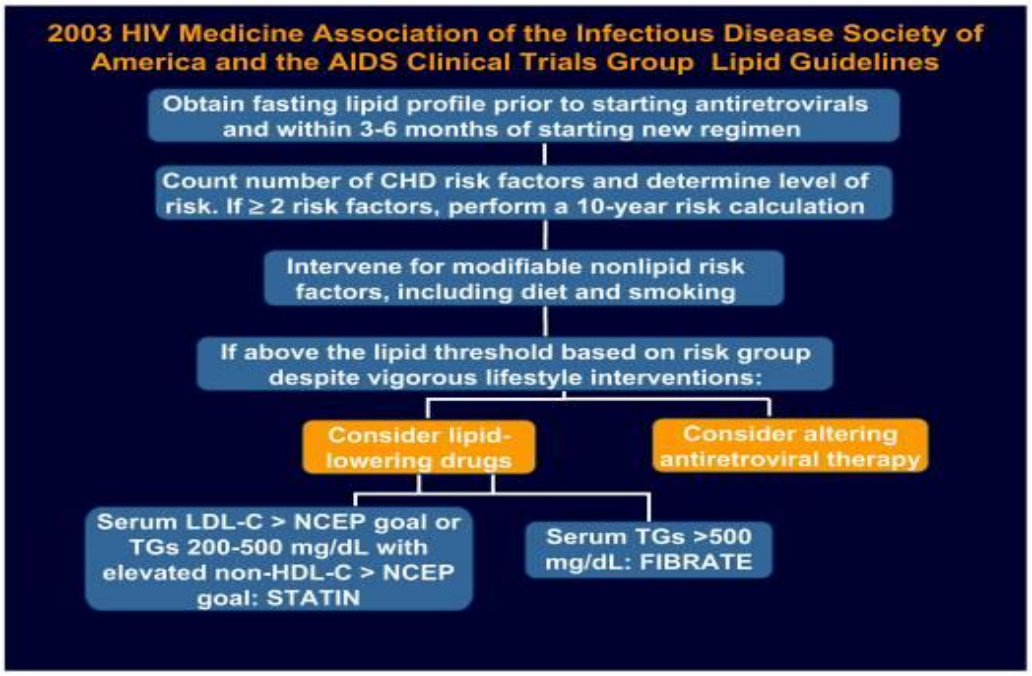

Figure 1

- 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. 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/mm^3. 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.

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Diabetes Mellitus in HIV and Aging

- The most important prevention for adult onset diabetes mellitus is to avoid excess weight gain. Since most HIV patients come into care at or below normal weight, patients initiating ART should be encouraged to avoid excess weight gain.
- Screening for diabetes should be done regularly, before and after the initiation of HAART, using glycosolated hemoglobin with appropriate diagnosis follow up. For patients with diabetes, glycosolated hemoglobin should be checked at least twice yearly.
- The target glycosolated hemoglobin (6.5% for younger patients) 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.

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. The incidence of diabetes increases with increasing age in the general population. The increase in risk in HAART- treated patients may be related to the use of certain antiretroviral drugs, such as thymidine analogues and protease inhibitors (lopinavir/ritonavir, indinavir, nelfinavir) (Llibre et al. 2009; De Wit et al. 2008). It appears that the new protease inhibitors and newer classes of antiretroviral drugs do not promote glucose intolerance. 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 HAART (Simone & Appelbaum 2008). There is some debate on whether screening should be done with fasting glucose levels or using glycosolated hemoglobin. Recently the American Diabetes Association has recommended that glycosolated hemoglobin is an acceptable screening tool, with a diagnosis of diabetes when the glycosolated hemoglobin is equal to or greater than 6.5% (American Diabetes Association, 2010). 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 glycosolated hemoglobin should be 6.5% for younger patients but 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 2010) . Recent studies have shown no benefit and possible harm from tight glucose control in type 2 diabetes mellitus (Wilson 2011). The glycosolated hemoglobin should be checked at least twice yearly. Care of HIV infected diabetics should focus on prevention of complications (such as foot ulcers, retinopathy, hypertension and vascular disease) as much as with HIV-uninfected patients. Renal function 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, 2006) 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 (lipoatrophy) and/or increase in central fat deposition (lipohypertrophy). Management options include switching HAART (removing thymidine analogues, using NNRTIs), surgical removal of fat, use of growth hormone or analogues.

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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 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.

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 begun on medications 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 involves having the patient return to clinic with all their medications and ensuring that the primary care provider has a complete list of meds prescribed by specialty providers. Annual medication reconciliation can also be facilitated by obtaining a complete dispensing history from the pharmacy. The accuracy of this list is increased if the patient uses one pharmacy or goes to a pharmacy that utilizes an integrated pharmacy computer network. The importance of critically assessing continued clinical need for each medication and a medication review cannot be overemphasized and should be done at every visit. Medication review/reconciliation provides an opportunity to determine which medications are no longer clinically indicated and may be discontinued to reduce the risk of toxicity and drug-drug interactions. Medication review, medication reconciliation and screening for toxicity and drug interactions are best facilitated by a clinically trained pharmacist. Electronic resources such as Epocrates, Lexi-Comp and Tarascon offer up-to-date interaction

checking (www.epocrates.com. www.lexi.com, www.tarascon.com).

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). 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.

Table 1: Common Medications Requiring Renal Dose Adjustment

Acyclovir
Clarithromycin
Co-trimoxazole
Fluconazole
Gabapentin
H_2-antagonists
Levofloxacin
Nucleoside RTIs (except abacavir)
Valacyclovir

Pharmacokinetic and pharmacodynamic changes

The difficulty with determining drug-drug interactions is that the studies are traditionally done in young, healthy, and occasionally 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 extent of an interaction will be at least as great as that observed in the study population. While no significant differences in pharmacokinetics (i.e. absorption, distribution, metabolism, excretion) have yet been found when studies have been conducted in aging individuals, other differences do exist that must be accounted for (Herrlinger & Klotz 2001; Klotz 2009; Onen et al. 2010).

Despite its shortcomings, the Cockcroft-Gault equation is still primarily used by the FDA, product package inserts and guidelines when drug dosing guidance is (Dowling et al. 2010; Lamb et al. 2003). 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, H_2-antagonists and most nucleoside RTIs (Table 1). Meperidine should be avoided in patients with renal insufficiency as should most non-steroidal

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 (diazepam, chlodiazepoxide, alprazolam)	Should be Avoided
Beta-agonists	Should be Avoided
Diphenyhydramine	Should be Avoided
Doxepin	Use with Caution
Fentanyle, oxycodone, morphine, methadone	Use with Caution
Meperidine	Should Be Avoided
Muscle Relaxants (carisoprodol, methocarbanol, baclofen	Use with Caution
Sedative hypnotics (zolpidem, others)	Should be Avoided
Temazepam, lorazepam	Should be Avoided
Tricyclic antidepressants	Should be Avoided

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 (α-blockers, β-blockers, β-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, H_2-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 pharmacokinetic/pharmacodynamic parameters or concomitant medical problems commonly experienced by aging patients.

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.

Table 3: Common Medications Interacting with Antiretrovirals
Azole antifungals (esp. itraconazole, posaconazole, voriconazole)
Fluticasone
H_2-antagonsits (when combined with atazanavir or rilpivirine)
HCVNS/4A inhibitords (boceprevir, telaprevir)
PDE5 inhibitors (esp. tadalafil)
Proton pump inhibitors (when combined with atazanavir or rilpivirine)
Rifabutin
Rifampin
Statins (esp. lovastatin and simvastatin)
Wafarin

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.

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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 from13.1% 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

	Studies	Cases	SIR	95% CL
Lung	13	847	2.6	2.1 to 3.1
Hodgkin lymphoma	13	643	11	8.8 to 15
Anus	8	253	28	21 to 35
Colorectal	4	174	1.1	0.69 to 1.7
Liver	11	171	5.6	4.0 to 7.7
Melanoma	10	161	1.2	0.88 to 1.6
Skin cancer	7	160	3.5	1.8 to 6.8
Prostate	9	159	0.69	0.55 to 0.86
Female breast	11	142	0.74	0.56 to 0.97
Kidney	9	109	1.7	1.3 to 2.2
Oropharynx	3	108	1.9	1.4 to 2.6
Leukemia	10	102	2.6	1.9 to 3.5
Stomach	11	96	1.7	1.2 to 2.5
Testis	8	96	1.4	1.1 to 1.9
Lip, oral, and pharynx	2	84	2.2	1.0 to 4.7
Brain	9	75	1.8	1.2 to 2.7
Multiple myeloma	9	72	2.6	1.5 to 4.5
Larynx	5	62	1.5	1.1 to 2.0
Esophagus	8	51	1.5	0.99 to 2.3
Bladder	9	48	1.1	0.72 to 1.7
Head and neck	4	42	2.0	1.1 to 3.6
Pancreas	9	39	1.0	0.74 to 1.4
Colon	4	26	0.81	0.48 to 1.4
Vagina	4	25	9.4	4.9 to 18
Thyroid	6	24	1.1	0.56 to 2.3
Penis	4	16	6.8	4.2 to 11
Rectum	2	16	1.5	0.54 to 4.2
Ovary	6	14	1.4	0.78 to 2.4
Uterus	4	14	1.5	0.68 to 3.4
Small intestine	3	10	2.2	1.4 to 3.3
Bone	5	7	2.6	1.3 to 5.0
Eye	2	7	3.1	1.6 to 5.9
Nasopharynx	2	7	4.1	2.1 to 7.9
Gall bladder	2	3	2.6	1.1 to 6.4
All non-AIDS cancers	9	3513	2.0	1.8 to 2.2

Table 5: From Shiels MS. *A Meta-Analysis of the Incidence of Non-AIDS Cancers in HIV-Infected individuals.*JAIDS:52(5);611-622 by Lippincott Williams & Wilkins. Reproduced with permission of Lippincott Williams & Wilkins in the format Journal via Copyright Clearance Center.

significant increased SIRs in five large published studies that were reviewed (Frisch et al. 2000; Frisch et al. 2001; Gallagher et al. 2001; 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.

Similarly, in a retrospective cohort study of HIV-infected and matched HIV-uninfected members of Kaiser Permanente followed between 1996 and 2007 for 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 **r**are 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 PNCSL. 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 2	Screening for HIV-negative	Organization & Year	Guideline HTML
Liver	Ultrasound +/- AFP; AFP only when ultrasound not available for individuals with chronic liver disease: q 6 mo.	AASDL 2010	http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf
Skin	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	Rec 1: ACS 2007; Rec 2: USPSTF 2009	ACS: http://www.cancer.org/Healthy/FindCancerEarly/CancerScreeningGuidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer USPSTF: http://www.uspreventiveservicestaskforce.org/uspstf/uspsskca.htm
Cervical	Cervical pap and in limited settings, HPV co-test.	Rec 1: ACOG 2009; Rec 2: USPSTF 2003; Rec 3: ACS 2002	ACOG: http://www.acog.org/publications/patient_education/bp085.cfm USPSTF:http://www.uspreventiveservicestaskforce.org/3rduspstf/cervcan/cervcanrr.htm; ACS: http://www.cancer.org/Healthy/FindCancerEarly/CancerScreeningGuidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer
Anal	No formal guidelines on screening.	No organizations endorse screening non-HIV-infected individuals for anal cancer	http://www.uptodate.com/online/content/abstract.do?topicKey=tumorhiv/2317&refNum=24,34
Lung	No national guidelines yet.	N/A	N/A
Breast	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, 70+ usinng screening mamography. 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.	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.	USPSTF: http://www.uspreventiveservicestaskforce.org/uspstf/uspsbrca.htm
CRC	For average-risk individuals beginning at age 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 75-85; do not screen over age 85; ACS, MSTF, & 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)**, or fecal immunochemical test (FIT) every year**, 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.	USPSTF 2008; ACS, MSTF and ACR 2008	USPSTF: http://www.uspreventiveservicestaskforce.org/uspstf08/colocancer/colosum.htm; ACS, MSTF, & ACR: http://www.cancer.org/Healthy/FindCancerEarly/CancerScreeningGuidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer

ACOG - American Congress of Obstetricians and Gynecologists
ACP - American College of Physicians
ACR - American College of Radiology
ACS - American Cancer Society
AMA - American Medical Association
USPSTF - U.S. Preventive Services Task Force
EACS - European AIDS Clinical Society
MSTF - 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

Table 3

Table 3	Screening for HIV-Positive	Organization & Year	Guideline HTML
Liver	Ultrasound +/- AFP; AFP only when ultrasound not available for individuals with chronic liver disease: q 6 mo.	AASDL 2010	http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf
Skin	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	N/A	N/A
Cervical	Cervical pap and in limited settings, HPV co-test.	CDC 2009	http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Anal	No formal guidelines on screening.	Rec 1 Palefsky 2009 Rec 2 NYS DOH 2009 Rec 3 EACS 2011	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19587592 http://www.health.ny.gov/diseases/aids/standards/index.htm http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-v6_english.pdf
Lung	No national guidelines yet.	N/A	N/A
Breast	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, 70+ 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.	N/A	N/A
CRC	For average-risk individuals beginning at age 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 75-85; do not screen over age 85; ACS, MSTF, & 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)**, or fecal immunochemical test (FIT) every year**, 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.	N/A	N/A

ACOG - American Congress of Obstetricians and Gynecologists
ACP - American College of Physicians
ACR - American College of Radiology
ACS - American Cancer Society
AMA - American Medical Association
USPSTF - U.S. Preventive Services Task Force

EACS - European AIDS Clinical Society
MSTF - 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

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Viral Hepatitis Screening in HIV and Aging

- All HIV-infected patients should be screened for hepatitis A, hepatitis B, and hepatitis C upon entry into care.

- Any unexplained elevations in liver enzymes should prompt a rescreening in those with negative screening tests at initial evaluation.
    - Screening for occult HBV can be considered in this setting, particularly in HCV-HIV coinfected patients. However, until there are more prospective studies on occult HBV disease, it is not practical to recommend general screening for this entity with HBV DNA testing on those without serologic evidence of chronic HBV infection.
    - Screening for acute HCV infection is important because therapy may be more effective and of shorter during than in chronic HCV-HIV coinfection. In addition, treatment of HCV may be improved with treatment at an earlier age.

- No formal recommendation can be made at this time for ongoing routine screening in asymptomatic HIV-seropositive patients at high risk for HCV. However, given increasing evidence of sexual transmission of HCV in high risk MSM populations, the increasing sexual activity among older individuals compared to the past, and the lower rates of sustained virologic response to HCV treatment in older patients, sexual behavior counseling as it relates to HCV transmission may be warranted in older individuals living with HIV.

- Screening for hepatocellular carcinoma in those with chronic HBV and HCV is discussed in the section on cancers. (see Cancer in HIV and Aging Section).

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.

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Chronic Obstructive Pulmonary Disease in HIV and Aging

- 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.

HIV-infected persons have an increased risk for several non-infectious pulmonary conditions including chronic obstructive pulmonary disease (COPD). COPD appears to present at younger ages in HIV-infected compared to HIV-uninfected patients (Crothers et al. 2011), suggesting that HIV infection accelerates aging-related decline in lung health, in parallel to other comorbid diseases (Deeks & Phillips 2009). 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).

The Global Initiative for Chronic Obstructive Lung Diseases defines COPD as "airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases" (Vestbo et al. 2009). The major risk factor for COPD is cigarette smoking, but occupational and environmental exposures also contribute. Among HIV-infected persons, COPD can occur at any CD4 cell count or HIV viral load. Prior bacterial pneumonia and *Pneumocystis* pneumonia are associated with airflow obstruction on pulmonary function testing (Morris et al. 2000).

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 (Vestbo et al. 2009). 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 (Vestbo et al. 2009). 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 with measurement of lung volumes and diffusing capacity should also be considered, as studies have found that HIV-infected patients may be particularly likely to have decreases in diffusing capacity with relatively normal spirometry (Gingo et al. 2010); decreased diffusing capacity suggests the presence of emphysema or other disease processes.

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 (Celli et al. 2004;Vestbo et al. 2009). In general, therapy is initiated for symptomatic COPD patients with inhaled short-acting

bronchodilators on an as-needed basis. For patients who have regular symptoms, long acting inhaled beta-agonists or anticholinergics are recommended. Inhaled steroids are generally reserved for patients with more severely impaired lung function (FEV1 less than 50% predicted) and with frequent yearly exacerbations.

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) 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 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, anxiety and (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. 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). In studies of HIV-uninfected patients with COPD, physical functioning is significantly improved with participation in pulmonary rehabilitation programs (Nici et al. 2006). 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.

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Sexual Health in HIV and Aging

- Consistent with the HIV 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.

Sexual health is broadly defined as more than just the absence of dysfunction or disease and includes the wide array of psychosocial and subjective meanings of sexuality. Sexual health is an important element contributing to the quality of life of older adults. 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). 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). Unless identified and addressed the sexual health of the older HIV+ patient will have a negative impact on health outcomes.

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; Arnsten & 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 fund 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.

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). This risk-taking is 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 with an existing ART in negative MSM subjects found a 44% reduction in the incidence of HIV (Grant et al. 2010). Such a regimen holds promise, but it will need to be replicated in other groups. For example treatment of an HIV-infected

partner of an HIV discordant pair has been shown to reduce significantly the rates of sexual transmission of HIV (Cohen et al. 2011).

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?

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Osteoporosis in HIV and Aging

- Since older patients have bone loss due to osteoporosis, and since many HIV-infected patients on HAART have accelerated bone loss, screening for (and aggressive treatment of) osteoporosis should be done .
- Since vitamin D deficiency is prevalent in older HIV-infected persons, screening for vitamin D deficiency is warranted

Osteoporotic bone disease adversely affects persons with advanced HIV infection disproportionately when compared to others of similar age. Bone density is lower, and the fracture rate is 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. In a study restricted to male veterans, Womack found that difference in BMI among those with and with HIV infection appeared to explain differences in fracture risk. 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 and smoking (McComsey et al. 2010; Qaseem et al. 2008). And separate from osteoporosis, HIV-infected persons are at increased risk of Vitamin D deficiency as well as other debilitating bone diseases such as avascular necrosis of weight-bearing joints (Mueller et al. 2010). Women of the age group considered by the panel (>50) are largely post-menopausal (which occurs at a younger age in HIV infection) (Schoenbaum et al. 2005); HIV-infected women should all receive routine, commonly-recognized screening and treatment for osteoporosis, as outlined in current guidelines for osteoporosis in the general population (AHRQ Guideline Summary 2007; Qaseem et al. 2008). Men of advanced age are increasingly recognized as being at risk for osteoporosis as well, due to androgen deficiency as well as the risk factors mentioned above (smoking, HAART, and nutritional factors) (Klein et al. 2005), and should be included in screening algorithms. Men should receive nutritional counseling if osteoporotic, and vitamin D supplementation if deficient. After reviewing risk factors for osteoporosis, attempts to modify those factors such as low BMI, smoking and use of proton pump inhibitors should be encouraged. Osteoporosis should be treated aggressively with conventional modalities appropriate to the individual patient. Androgen supplementation would be an individual decision between patient and provider and was not deliberated by the Panel.

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The Kidney in HIV and Aging

- Older individuals should have annual measurements of serum creatinine, eGFR and urinary protein excretion, including those with known HIV infection.
- All older individuals with a history of injection drug abuse or new onset proteinuria should be screened for HIV and other infections (e.g. HCV, HBV, SBE).
- Individuals with an acute change in kidney function need to be evaluated for all causes of kidney disease. Because of the broad differential diagnosis in older, HIV-infected persons, consultation with a nephrologist is appropriate, and kidney biopsy may be indicated.
- Careful consideration of the need to adjust drug dosage of all medications in all older persons is essential.
- Older HIV-infected persons with CKD of known etiology who are being managed by current NKF KDOQI guidelines should be referred for discussions of renal replacement therapy (dialysis or transplantation) when eGFR reaches 15-29 ml/min. As in all individuals evaluated for renal replacement therapy, issues of comorbidities, life expectancy, and functional status should be considered during joint decision making.
- Kidney disease dramatically increases the risk of myocardial infarction. Patients with eGFR<30 should be aggressively managed to minimize risk of MI.
- Hypertension is a major cause of kidney disease in the aging population. Patients demonstrating evidence of decreasing eGFR should have aggressive management of their hypertension.

Measurement of serum creatinine is the most common correlate of filtration function of the kidney. Current methods for measuring serum creatinine are both sensitive and specific, and under clinically stable conditions vary < 0.2mg/dL. Increases of greater than 0.2 mg/dL indicate a significant change in kidney function and require some attention. Changes in serum creatinine that are due to a modest change in renal perfusion (e.g. medications, volume depletion), usually occur only in individuals with underlying, compensated kidney disease, and usually revert to baseline when renal perfusion is restored to pre-existing levels. Significant or progressive increases in serum creatinine more often indicate progression of known underlying disease or superimposition of a significant additional diagnosis that requires evaluation. Glomerular filtration rate (eGFR) is usually estimated from serum creatinine using either the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) formula. In all cases, estimates of GFR are valid only in steady-state conditions where serum creatinine is stable. The primary utility of eGFR is in making dosing adjustments for renal excreted drugs or in establishing the stage of chronic kidney disease (CKD) progression in individuals with a known CKD diagnosis. Beginning at CKD Stage 3 (eGFR < 60ml/min), individuals develop progressive risk for CKD complications (anemia, bone disease, hypertension, volume

retention, etc) that may require additional attention and interventions. At CKD Stage 4 (eGFR 15-29 ml/min) evaluation and planning for kidney replacement therapy (dialysis or transplantation) needs to begin. This includes a potential determination that based on functional status or the presence of other terminal conditions renal replacement therapy is not appropriate. At CKD Stage 5 (eGFR < 15 ml/min), uremic symptoms may develop, and where appropriate, dialysis or transplantation should occur.

In addition to loss of filtration capacity, proteinuria is an indicator of both presence of and risk for progression of kidney disease. Proteinuria is a common presenting manifestation of HIV-associated nephropathy (HIVN), as well as glomerular diseases common to older individuals or HIV-seropositive individuals with other infections (e.g streptococcal, HCV, HBV) (Appel 2007; Elewa et al. 2011). Therefore, the urine dipstick for protein is a good screening test for the presence of asymptomatic kidney disease, as well as a predictor of those likely to develop progressive loss of kidney function.

Kidney disease and mortality in HIV-infected persons: Chronic progressive kidney (CKD) disease significantly contributes to a shortened life span in all populations, and HIV-infected persons with evidence of kidney dysfunction have worse outcomes than those with normal kidney function (Estrella & Fine 2010; Yanik et al. 2010). The presence of kidney disease contributes to increased frailty, and increased mortality following hospitalization for all other causes. For these reasons, identification and management of CKD is critically important to improve the outcomes of all HIV-infected persons.

Aging nephropathy and other kidney diseases in older persons

With advancing age the kidney develops aging nephropathy that is characterized by progressive glomerulosclerosis and tubulointerstitial fibrosis even in the absence of other specific forms of kidney disease (Rule et al. 2010). In individuals with aging nephropathy and relatively preserved kidney function (eGFR > 60 ml/min), there is still an increased risk for rapid fibrosis and end-stage kidney disease (ESKD) when any other type of kidney disease is superimposed (e.g. acute kidney injury, HIV-nephropathy, HCV nephropathy, post-infectious glomerular disease) (Venkatachalam., 2010). Furthermore, the presence of proteinuria and/or reduced GFR (eGFR < 60 ml/min) increases the risk for accelerated cardiovascular disease, frailty, and morbidity and mortality when individuals are hospitalized for any other cause. Thus, older persons with HIV must be presumed to have increased risk for developing significant chronic kidney disease and its associated complications. Unlike most forms of glomerular disease that primarily affect young individuals, membranous nephropathy and ANCA+ rapidly progressive glomerulonephritis occur predominantly in older persons (Abrass 2003). HIV-infected individuals may also have HCV, HBV or other infections that can cause kidney disease. Thus, older HIV-infected persons are particularly prone to altered kidney function from a variety of causes. Specific kidney diseases other than HIVN may go undiagnosed because changes in eGFR or proteinuria are erroneously attributed to identified co-existing diagnoses (e.g. heart failure, diabetes mellitus). Accurate diagnosis of the cause(s) of altered kidney function requires kidney biopsy. Neither age nor HIV status per se should alter the criteria for performing a kidney biopsy (Abrass 2000).

HIV nephropathy (HIVN)

HIVN results from direct infection of the glomerular podocyte with HIV, and it is associated with proteinuria, viral load, and degree of immunosuppression (Wyatt et al. 2009). Although severe nephrotic syndrome and rapid progression to ESKD is less common in HAART-treated individuals, proteinuria and CKD are still prevalent (approximately 30%), and another 50% have sub-clinical kidney pathology (Wyatt et al. 2009). Women and African Americans have higher rates of HIV nephropathy as compared to other HIV-infected individuals. Furthermore, individuals with proteinuria are more likely to be infected with HIV (Yanik et al. 2010); thus, evidence of kidney disease may be the presenting manifestation of HIV infection. HAART therapy preserves kidney function in individuals with HIVN. There is some evidence that HAART therapy per se may be nephrotoxic. Protease inhibitors (indinavir and atazanavir) are associated with crystal-induced obstruction, and reverse transcriptase inhibitor (tenofovir) may cause acute kidney injury with reductions in eGFR or Fanconi syndrome (Izzedine et al. 2009). Although potential drug toxicities need to be considered in HIV therapy, the benefits of HAART justify their continued use. When acute kidney injury is superimposed on pre-existing, often unrecognized, kidney disease, CKD may rapidly develop after recovery from the acute event (Izzedine et al. 2009; Venkatachalam et al. 2010). Given that up to 90% of individuals over the age of 70, even those with eGFR>60 ml/min have significant histological evidence of kidney fibrosis (Rule et al. 2010), these concerns may apply to all older individuals with HIV. Furthermore, there is evidence that development of AIDS-defining illnesses is hastened in the presence of kidney dysfunction, and that earlier treatment with HAART may delay the onset/progression of HIVN; thus, screening for HIVN and institution of HAART in those with evidence of HIVN may be appropriate prior to meeting other criteria for HAART (Szczech 2009). There is substantial evidence for genetic susceptibility to ESKD (Tzur et al. 2010; Winkler et al. 2010). Polymorphisms in the non-coding region of the myosin heavy chain gene (MYH9) and the nearby APOL1 gene are highly associated with a significant risk for developing progressive forms of kidney disease, particularly among blacks. Evidence suggesting a similar confluence of risk in diabetic nephropathy and HIVN is less clear; yet, it has been proposed that HIV+ individuals be screened for this genetic risk with consideration for earlier initiation of HAART (Winkler et al. 2010).

Kidney replacement therapy

Currently, more than 65% of all new dialysis patients are over age 65; thus, significant loss of kidney function is an important concern among all older persons (Venkatachalam et al. 2010). As HIV-infected persons age their risk for ESKD is expected to be higher than uninfected persons. Ageism and biases related to HIV infection can contribute to delayed diagnosis of kidney disease and late referral for kidney replacement therapy. Studies of older persons per se indicate that they should be evaluated, referred for kidney biopsy, and treated based on diagnosis using the same criteria as those used in younger individuals (Abrass, 2000). Older individuals have more difficulties with vascular access, are more prone to heart failure and have enhanced frailty as CKD progresses. These factors may be aggravated by concomitant HIV infection; thus, early referral for consideration for future dialysis planning and access placement is critical to improve outcomes for these individuals. Although there are no data specifically addressing transplantation in older, HIV-infected persons, good outcomes have been achieved

in the elderly and HIV-infected individuals (Reese et al. 2010). Current recommendations indicate that HIV-infected individuals should be considered for transplantation using the same criteria as in other individuals (Stock et al. 2010) (Levey et al. 2003). However, as transplantation guidelines undergo continuous revision, consultation at the time of consideration for transplantation is essential.

Drug Toxicity

Reduced kidney function alters drug clearance and affects drug-drug interactions. Both changes increase risk for enhanced nephrotoxicity, other drug side effects and toxicities (Hajjar et al. 2007). Unrecognized reductions in kidney function are an important contributor to adverse drug events, which are particularly common in older persons receiving multiple mediations. With each new medication, the impact of reduced kidney function needs to be considered, and drug interactions and dosages adjusted accordingly. The importance of these principles has also been emphasized in the management of HIV-infected individuals with ESKD (Novak & Szczech 2010).

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Hypertension in HIV and Aging

- Hypertension should be treated in older HIV-infected individuals using recommended guidelines and goals, with avoidance of pressures <130/70 mmHg.
- Although some individuals, particularly older individuals, lack evidence of activation of the renin-angiotensin-aldosterone system, they may still respond to angiotensin converting enzyme inhibitors and angiotensin receptor blockers. As these agents confer better risk reductions for cardiovascular events and ESKD, their use may be considered in all individuals with hypertension.
- Because of the increased risk for orthostatic hypotension, and electrolyte abnormalities, treatment of hypertension in older persons should be initiated with low doses of medication and monitoring for side effects before increasing the dose to achieve therapeutic goals.

Hypertension, characterized by a widened pulse pressure with an increase in systolic and decrease in diastolic blood pressure, is prevalent among older persons affecting three-quarters of individuals over the age of 75. Arterial fibrosis is associated with a reduction in compliance which contributes to the widened pulse pressure. Increased salt sensitivity is influenced by altered excretion of salt by the kidney that is mediated by a variety of intra-renal changes associated with aging nephropathy (Rao & Bakris 2011) and contributes to the development of hypertension.

Systolic blood pressure is a predictor of cardiovascular events and ESKD (Young et al. 2002), and there is strong evidence and consensus that treating high blood pressure reduces morbidity and mortality, including in older persons (Rashidi & Wright 2009). Benefits of treatment to prevent significant morbidity and mortality from cardiovascular disease are achieved within 2-5 years (Rakugi et al. 2010); thus, most older persons, including those with HIV, who have hypertension, should be treated.

Over many years, various target blood pressures have been advocated and examined. Recent trends to achieve pharmacological reductions in systolic blood pressure (SBP) to levels of 120 or below have been challenged, particularly in the elderly. Results from the Systolic Hypertension in the Elderly Program (SHEP) (Fogari & Zoppi 2004) and additional retrospective studies indicate that reductions in systolic pressure below 130 or diastolic pressure below 60-65 mmHg are associated with higher cardiovascular event rates in older persons (Fogari & Zoppi 2004); thus, Bakris (Bakris et al. 2010; Rao & Bakris 2011) has suggested treatment goals in the elderly that do not go below 130/70. As there are no specific studies to address treatment targets in HIV-infected older persons, JNC guidelines represent a consensus that provides goals and step-wise approaches. Based on these guidelines, most physicians strive to reduce blood pressure to less than 140/90 mmHg. It is uncertain whether reductions beyond this level are beneficial or harmful, or which specific individuals should be managed differently, such as older (over age 50) HIV-infected individuals.

Older persons with hypertension have been shown to benefit from a variety of approaches including sodium restriction (< 2g/d), weight loss (10 pounds) (Whelton et al. 1998), and reductions in intake of non-steroidal anti-inflammatory drugs (Whelton et al. 2002). Pharmacologic treatment with reductions in blood pressure to less than 150/80 even in individuals over the age of 80 have been associated with reduced risk for cardiovascular events and stroke (Beckett et al. 2008). Based on a variety of trials 28-31 several generalizations have been noted that apply to older persons. As single agents, calcium antagonists and thiazide diuretics provide more consistent reductions in blood pressure than do other classes of drugs. Yet, two or more agents are almost always required for adequate management of hypertension in older (Jamerson et al. 2008; Wing et al. 2003). Although there are reductions in activity of the renin-angiotensin-aldosterone system in older persons, anti-hypertensive agents that affect this system are still effective in older persons, and may provide better risk reduction for stroke and cardiovascular events (Rashidi & Wright 2009). Recent data showing that angiotensin-converting enzyme inhibitors reduce blood pressure by mechanisms in addition to effects on angiotensin II levels provide evidence for efficacy of these agents even in low-renin states (Rashidi & Wright 2009). Aside from the increased risk for pulmonary hypertension and cardiac disease with diastolic dysfunction, there is no evidence that HIV infection per se affects systemic blood pressure; thus, usual recommendations in older persons should apply.

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Older Age and HIV-Associated Neurocognitive Disorder (HAND)

- 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 likely 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.

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 or HAD, but without any functional status deficit. These 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 deems cognitive screening to be clinically important. Quick and simple screening instruments exist for the most severe form of HAD, 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.

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(Power et al. 1995) (Power et al. 1995) 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. A recent publication provides a more complete review of these instruments for HIV(Valcour et al. 2011).

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). 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 are 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, remaining socially engaged, monitoring for depression, and monitoring for cerebrovascular risk factors are relatively safe and possibly effective adjunctive strategies.

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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 co-factor in examining a depression diathesis in the older HIV infected persons (Shippy & Karpiak 2005; Shippy & Karpiak 2005). 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).

The elevated physical symptom burden associated with depressive disorders and suicide risk may be further enhanced by psychoactive substance use and elevated pain level (Tsao et al. 2005) as well as with other psychiatric disorders and substance use disorders generally are at high risk for major depressive disorder (Berger-Greenstein et al. 2007), and 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). 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.

Anxiety Disorders in HIV and Aging

- Many anxiety disorders can be addressed with SSRIs rather than benzodiazipines with fewer adverse consequences.
- If pharmacotherapy is indicated for acute control of anxiety, the short- to intermediate-acting benzodiazepines with no active metabolites are preferred.
- Non-benzodiazepine agents are preferred for longer-term anxiety control, when longer-term pharmacotherapy is judged to be warranted.

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. As noted above, 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). 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.

Substance Use Disorders

- Patients should be encouraged to discontinue or minimize their alcohol and substance use and be referred to a counseling program if found to have abuse or dependence disorders.

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. Yet, illicit drug use is 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 is due to increased cannabis use in younger patients. Non-cannabis drug use frequency is almost exactly the same in older and younger HIV infected patients.. 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, 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. The co-occurrence of substance use with mental health issues is clear, but also it is a significant factor in the co-morbidities 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.

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HIV-1 Associated Peripheral Neuropathologies in HIV and Aging

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-1 infected, occurring in from 35% to 67% of patients. 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). However, data have implicated the protease inhibitors as well (Lichtenstein et al. 2005). Mitochondrial toxicity has been suggested as a mechanism, as well as dyslipidemia. 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 – infrequently to 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 (Simpson et al, 1998a); however, it 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. 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. Moreover, individuals taking statin drugs are more likely to have elevated triglyceride levels ─ potentially mediating the associated DSP. In addition, patients with HCV co-infection are at risk for DSP, though this co-morbidity 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. 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). Moreover, amtriptyline was specifically not shown to be more effective than placebo in ACTG 242 (Kieburtz et al. 1998). 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; carbamazepine has also been used 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.1998b) followed by a subsequent larger study (Simpson et al. 2003). Lidocaine gel (5%) initially showed promise in an open label study but failed in a controlled clinical trial (Estanislao et al. 2004). Most recently, a high-dose capsaicin patch has shown controlled evidence for its use in a sample of good size (Simpson et al. 2008). It should be noted that use of the foregoing medications frequently does not achieve a level of pain control that satisfies the patient and that 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.

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Advance Care Planning in HIV and Aging

Older HIV-infected patients, especially those with substantial illness burden, should be counseled in completing a durable power of attorney for health care and an advance directive such as the "Physician Orders for Life Sustaining Treatment" or POLST form.

Two decades ago 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). Then, when HIV infection was clearly more life-threatening, it was incumbent upon everyone involved in the care of these patients to insure that they had considered advance care planning and surrogate decision-making as a routine part of care. It was common, early in the epidemic, for HIV-infected patients receiving regular medical care to have a durable power of attorney for healthcare and an advance directive or living will (Steinbrook et al. 1986). Over the past decade this practice has fallen by the wayside to some extent as persons with HIV infection have led healthier, functional lives on effective therapy (Wenger et al. 2001).

For persons with advancing age and long-standing HIV infection, particularly those with even modest cognitive or functional impairment, 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 important medical decisions for them in the event of serious illness. And, over the past 2 decades, the 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 POLST (2010) form, 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).

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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..

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Disclosures

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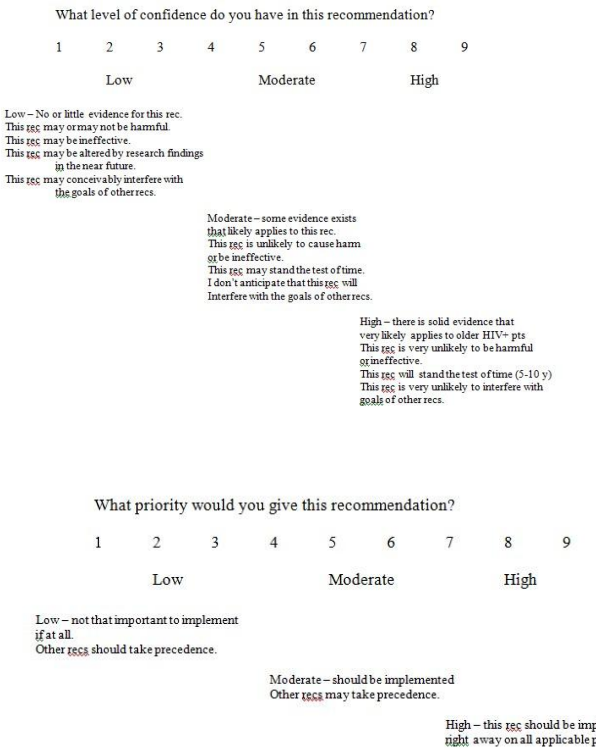
Appendix


What level of confidence do you have in this recommendation?
1 2 3 4 5 6 7 8 9
Low
Moderate
High
Low – No or little evidence for this rec.
This rec may or may not be harmful.
This rec may be ineffective.
This rec may be altered by research findings in the near future.
This rec may conceivably interfere with the goals of other recs.
Moderate – some evidence exists that likely applies to this rec.
This rec is unlikely to cause harm or be ineffective.
This rec may stand the test of time.
I don't anticipate that this rec will Interfere with the goals of other recs.
High – there is solid evidence that very likely applies to older HIV+ pts
This rec is very unlikely to be harmful or ineffective.
This rec will stand the test of time (5-10 y)
This rec is very unlikely to interfere with goals of other recs.
What priority would you give this recommendation?
1 2 3 4 5 6 7 8 9
Low
Moderate
High
Low – not that important to implement if at all.
Other recs should take precedence.
Moderate – should be implemented
Other recs may take precedence.
High – this rec should be imp
right away on all applicable p