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Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome in Older Adults

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Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

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Key words: Human Immunodeficiency Virus, Acquired Immunodeficiency Syndrome, antiretroviral therapy, Immunocompromised host, Epidemiology

Key points

- The population of older HIV-infected patients increasing. By 2020 over 50% of HIV-infected persons in the US will be older than 50 years of age
- Untreated older HIV-infected patients progress more rapidly to AIDS and higher mortality rates
- Patients up to age 64 should be routinely offered HIV testing; testing up to age 75 is recommended for adults who might transmit HIV to others.
- The occurrence of co-morbidities not traditionally associated with HIV infection now exceeds that of AIDS-related events and are especially relevant to older patients
- ART should be offered to all HIV-infected patients regardless of age, symptoms, CD4+ cell count or HIV viral load. Early treatment is especially important in older patients

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Synopsis

Improved survival with combination antiretroviral therapy has led to a dramatic rise in the number of HIV-infected individuals ≥50 years of age such that by 2020 more than 50% of HIV-infected persons in the United States will be above this age. Recent studies confirm that ART should be offered to all HIV infected patients regardless of age, symptoms, CD4+ cell count or HIV viral load. However, when compared to HIV-uninfected populations even with suppression of measurable HIV replication older individuals are at greater risk for cardiovascular disease, malignancies, liver disease and other co-morbidities. The risk of these HIV-Associated Non-AIDS (HANA) conditions reflects the effects of incomplete immune reconstitution, residual inflammatory responses and drug toxicity. Unfortunately, older HIV-infected individuals disproportionately suffer from delayed HIV diagnosis because of decreased awareness of the importance of routine HIV testing in this population. Optimal care of the aging HIV-infected population will increasingly require the skills of generalists, HIV specialists and geriatricians.

Introduction

The development of better-tolerated and more efficacious combined antiretroviral therapy (ART) has transformed what was once an inexorably progressive illness into a manageable chronic disease for which life expectancy has begun to approach that of the general population. This substantial increase in survival has led to a steady rise in the number of HIV-infected individuals who are older than 50 years of age. This demographic change is coupled with substantial clinical issues unique to older HIV infected persons provides important challenges to clinicians caring for older patients.

Epidemiology

In 2012, 40% of all HIV-infected persons in the United States were ≥50 years of age; by 2020 more than 50% of HIV-infected persons will have reached this age.[1;2] Aging of the HIV-infected population is not unique to the developed world. The World Health Organization estimates that as of 2014, there were an 4.2 million people in the world living with HIV who were over age 50; most of these people are in Sub-Saharan Africa (Figure 1).[3]

Natural History of HIV Infection in Older Patients

After infection, initial plasma HIV-1 RNA levels (viral load) are higher and CD4+ cell counts are lower in older patients than in younger patients. Subsequently, the rate of decline of CD4+ cells is greater in older patients resulting in a more rapid progression to AIDS and death. Although the major complications of HIV infection generally occur after the CD4+ count drops to <200 cells/□L, older individuals have higher rates of AIDS-defining events than do younger individuals at any given CD4+ cell count.[4]

Diagnosis of HIV infection and Case Identification

The United States Preventive Services Task Force recommends that all patients aged 13 to 64 be offered HIV testing at least once-per-lifetime as a part of routine medical care and regardless of known or perceived risk.[5] An exception to the recommendation was made for populations in which the prevalence of undiagnosed HIV infection is known to be < 0.1%. Furthermore, the American College of Physicians (ACP) recommends offering testing up to age 75 for persons who might, if infected, transmit HIV to others.[6]

In addition, to once-per-lifetime testing, high-risk individuals, such as men who have sex with men, injection-drug users, and sex partners of HIV-infected persons, should have annual or more frequent testing. Targeted testing is also indicated for patients with a potential recent high-risk event or with unexplained symptoms consistent with HIV infection, including weight loss, unexplained dementia, mucosal candidiasis or AIDS-defining opportunistic infections or malignancies.

As of 2012, 13% of the estimated 1.2 million persons infected with HIV in the US remained unaware of their diagnosis; 5% of the undiagnosed population was ≥55 years of age.[7] Among HIV-infected individuals over age 50-55, the median duration of infection prior to diagnosis is estimated to be 6.8 years.[8]

Delayed testing for HIV infection in older patients stems from a number of different factors. Because of lack of awareness older individuals are less likely to request HIV testing and healthcare providers are less likely to offer routine testing. Finally, targeted testing is often delayed because older HIV infected individuals often present with non-specific manifestations such as gradually worsening weight loss and fatigue that mimics other maladies.[9]

Delays in testing contributes to the fact that older HIV-infected patients are more likely to have progressed to full-blown AIDS when they are diagnosed (Figure 2) and are much more likely to die within 1 – 3 years of their diagnosis than are younger adults (Figure 3).[2]

Treatment

Combination ART has led to decreased rates of the opportunistic infections and malignancies traditionally associated with HIV infection as well as to decreases in the incidence of HIV-associated non-AIDS (HANA) co-morbidities such as cardiovascular disease, the metabolic syndrome, diabetes, liver disease, kidney disease, neurologic disease and non-AIDS-related malignancies.[10;11] ART achieves these goals by suppressing HIV replication thereby restoring immunologic function. Of great societal importance is effective ART also markedly decreases the risk of HIV transmission by infected individuals.[10]

Timing of Initiation of ART

Clinical trials have led to a long-standing strong recommendation that ART should be initiated in asymptomatic HIV-infected persons with < 350 CD4+ cells/□L or with a history of an AIDS-defining illness. Although recommendations for starting therapy at higher CD4+ cells have been more moderate, recent clinical trials have now conclusively demonstrated that ART reduces HIV-related and overall morbidity and mortality regardless of the CD4+ cell count or viral load when therapy is initiated.[12] In particular, the recently concluded START trial demonstrated that immediate initiation of ART in patients with CD4+ cell counts over 500 cells/□L is superior to the deferral of ART until the CD4+ cell count declines to less than 350 cells/□L.[11] The benefits of the immediate therapy include lower rates of serious AIDS-related and serious non-AIDS-related events (i.e., HANA); the benefits did not differ according to age, sex, race, CD4+ cell count, viral load, or risk factors for serious non-AIDS diseases. While only 25%

of the subjects were older than 44 years of age, it is highly unlikely that any future randomized control trial data will be available for yet older patients.

Based on these trial results, updated authoritative guidelines now strongly recommend that ART be initiated in all individuals who are willing and ready to start therapy regardless of their CD4+ cell count or age.[12] The guidelines specifically advocate for universal ART in HIV-infected persons over age 50, regardless of their immune status, since "the risk of non-AIDS related complications may increase and the immunologic response to ART may be reduced in older HIV-infected patients".[10]

Consequently, while taking into consideration co-morbidities, drug-drug interactions, polypharmacy, patient preference and readiness to be adherent to therapy, providers should now offer ART to all patients regardless of age or CD4+ cell count. Deferrals of therapy, such as for patients who require a change in their baseline medications due to clinically significant drug-drug interactions with ART or for persons with serious barriers to adherence should be brief, especially in persons with <200 CD4+ cells/□L.[10]

Selection of therapy

Although the six classes of antiretroviral agents include over two dozen individual agents, only five regimens are recommended for initial therapy (Table 1). Based on safety and efficacy, regimens containing a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a PI other darunavir are no longer regarded as first line regimens for ART-treatment-naïve patients.[10]

The choice of the antiretroviral regimen should take into consideration, the patient's existing viral load, CD4+ cell count and resistance testing results, and the agent's virologic efficacy, toxicity, pill burden, dosing frequency and potential for drug-drug interactions. In

addition, it is important to consider the adverse effects of antiretroviral agents on any pre-existing co-morbidities (Table 2).[10]

Response to therapy

When started on effective therapy, adherent patients achieve at least a 90% (one-log) reduction in the plasma HIV-1 RNA concentration (viral load) within one month of initiating therapy. The viral load should decrease to less than 400 HIV-1 RNA copies/mL in 3 months. A viral load persistently less than 200 HIV-1 RNA copies/mL represents treatment success; this is should be achieved within 6 months of treatment initiation. Failure to achieve these virological outcomes represents treatment failure due to non-adherence and/or antiretroviral resistance. Management of patients with treatment failure should be in coordination with a specialist in HIV care and is beyond the scope of this review. Comprehensive treatment recommendations are available at http://aidsinfo.nih.gov/guidelines.

Pathophysiologic effects of long-term HIV infection

Compared to uninfected individuals, even patients with excellent virological and immunological responses to treatment remain at increased risk for a wide variety of HANA complications.[10;13] Indeed, the overall morbidity and mortality related to comorbidities now exceeds those of AIDS-related events.[14]

Although increased rates of cigarette, alcohol and recreational drug use are important contributors to the occurrence of HANA co-morbidities, the contribution of HIV-related immune activation and inflammation has become increasingly apparent as elevated levels of inflammatory and coagulation biomarkers such as hsCRP, IL-6 and d-dimer are associated with increased risk of all-cause mortality and non-AIDS-defining events. Although the highest levels of immune activation and inflammation are seen among individuals with uncontrolled HIV

replication, these phenomena persist, albeit at generally lower levels, and predict the occurrence of poor clinical outcomes despite effective viral suppression.[13]

HIV-Associated, non-AIDS Complications (HANA)

Cardiovascular disease is a particularly important and complex issue affecting HIV-infected patients. Although various ART regimens have been associated with metabolic disturbances that increase the risk of cardiovascular disease, effective ART lowers the risk of cardiovascular disease.[15] Nonetheless, even with effective ART, the risk of cardiovascular disease is approximately 50% higher in HIV-infected persons than in uninfected control populations.[16] Importantly, the increased risk of myocardial infarction is not fully accounted for by other comorbidities, or substance use, or by the Framingham or other risk calculators.[16] In addition, HIV infected patients have increased rates of hypertension, heart failure, sudden death and cerebrovascular events.

The causes and mechanisms leading to increased risk of cardiovascular disease in HIV-infected patients represent a complex interplay between pre-existing cardiovascular risk factors, HIV infection, chronic inflammation, and ART. Some PIs (e.g., lopinavir-ritonavir and indinavir) but not others (atazanavir) are independently associated with increased risk of myocardial infarction.[17] While not shown in randomized, controlled clinical trials done in low-risk, relatively young patients,[18] retrospective studies done in older patients have found that abacavir, a commonly used NRTI, is associated with an increased cardiovascular disease risk.[19]

The adjusted rate of incident diabetes has been reported to be 4-fold higher among HIV-infected men receiving ART than among uninfected men. Implicated agents include NRTIs and PIs that are now less commonly used e.g., stavudine, didanosine, zidovudine, indinavir and

lopinavir/ritonavir.[20] Whether there is an association between newer ART agents or between HIV infection p*er se* and increased risk of diabetes remains unclear.[20]

Fat redistribution, i.e., lipoatrophy (loss of subcutaneous fat) and lipohypertrophy (visceral fat accumulation) commonly affects those infected with HIV and has been associated with insulin resistance, abnormal lipid metabolism, hypertension and increased mortality.[21] Mitochondrial DNA toxicity associated with NRTIs, especially with drugs used more often in prior years such as didanosine, stavudine and zidovudine, has been proposed as a cause of lipoatrophy.[22]

Untreated HIV infection is associated with increased triglycerides and decreased high density and low density lipoproteins, that can improves after the initiation of ART, particularly among persons with a normal baseline body mass index.[23] However, some commonly used antiretroviral drugs are associated with hyperlipidemia including selected ritonavir-boosted PIs, efavirenz, and elvitegravir/cobicistat-containing regimens; other NNRTIs, INSTIs, and tenofovir are associated with less deleterious effects.[10]

Approximately 25% of HIV infected patients have previously been reported to have the metabolic syndrome, i.e. abdominal obesity, dyslipidemia, hypertension, and insulin resistance.[20] Risk factors include the use of PIs, particularly lopinavir/ritonavir, stavudine and didanosine, and unsuppressed HIV replication.[24]

Liver disease is a significant cause of mortality in patients with HIV. Risk factors for liver disease include low CD4+ cell counts, uncontrolled HIV infection, and intravenous drug use, as well as active hepatitis B or C virus (HBV and HCV, respectively) infection.[25] HBV and HCV are particularly important given their high prevalence in HIV-infected patients. Effective treatment for both HIV and HCV decreases the rates of liver-related mortality and death in co-

infected patients while HBV co-infection is an important consideration in the selection of antiretroviral therapy.[10] In addition, life-threatening hepatotoxicity reactions can occur as a consequence of hypersensitivity reactions (i.e., nevirapine) or as a consequence of lactic acidosis and steatosis (e.g., with use of stavudine, didanosine and zidovudine).

HIV-infected patients are at high risk for chronic kidney disease and end-stage renal disease.[26] Risk factors for kidney injury that are specific for HIV include ART-related nephrotoxicities, HCV co-infection, lower CD4+ cell count, and higher HIV RNA levels.[27] HIV medications that are particularly associated with kidney injury include specific PIs (i.e., indinavir, lopinavir/ritonavir and atazanavir) and tenofovir disoproxil fumarate. HIV-infected African-Americans are at particular risk for developing advanced kidney disease due to their susceptibility to HIV-related nephropathy.[26]. When choosing combination ART for patients with chronic kidney disease, use of the older formulation of tenofovir (tenofovir disoproxil fumarate), especially in combination with a PI, should be avoided if possible. Of note, tenofovir alafenamide, a new formulation of tenofovir, is associated with lower rates of nephrotoxicity.[28]

The incidence of AIDS-defining cancers has decreased since the beginning of the AIDS epidemic. However, the incidences of many non-AIDS defining cancers (e.g., lung, liver, colorectal, melanoma, anal, head and neck cancers and of Hodgkin's lymphoma) have increased since the introduction of ART.[29] Some cancers (mainly anal cancer, liver cancer and Hodgkin's lymphoma) occur at younger ages in those infected with HIV compared to those without HIV.[30]

Osteoporosis and fragility-related fractures occur more often in HIV-infected persons. Factors shown to contribute to higher rates of bone disease in people with HIV infection include the use of tenofovir disoproxil fumarate and possibly PIs (particularly lopinavir/ritonavir), lifestyle differences such as tobacco smoking, alcohol or substance abuse, low body mass index,

coinfection with hepatitis C, use of proton pump inhibitors, diabetes, vascular disease, and older age.[31] Tenofovir alafenamide is associated with lower rates of bone demineralization than is tenofovir disoproxil fumarate.[28]

Neurocognitive deficits are significantly more common in HIV-infected individuals and range from asymptomatic neurocognitive impairment to HIV-associated dementia (HAD). HAD is typically manifested as impaired attention and concentration, apathy, and impaired motor skills.[32] Although neurocognitive deficits predominate in untreated patients with advanced HIV/AIDS, mild cognitive deficits frequently occur in patients with well-controlled HIV. Of critical importance is that HIV-related neurocognitive disorders can dramatically respond to effective anti-retroviral therapy and are often the presenting manifestations of HIV infection, especially among older patients.

HIV infection is independently associated with increased rates of chronic obstructive pulmonary disease, emphysema, bacterial pneumonia and pulmonary hypertension, and accelerates the rate of complications seen with smoking.[33]. Risk factors for pulmonary dysfunction among HIV-infected individuals include more advanced HIV infection and elevated soluble CD14 levels, a measure of immune activation.[34]

Finally, an accelerated rate of frailty, characterized by weight loss, weakness, exhaustion, low physical activity, and slowness has been observed in people with HIV infection compared to HIV uninfected individuals. Factors associated with increased rates of frailty in persons with HIV infection include CD4+ cell count, HIV RNA level, increased age, and low BMI.[35]

Prevention of HIV Infection

Older individuals often fail to see themselves at risk for HIV, a misperception that is unfortunately shared by many clinicians. In general, public educational messages and

intervention strategies about HIV prevention focus more on the younger population. Moreover, older adults may be reluctant to talk about sex, and institutions frequented by older adults, such as churches, senior centers, and retirement communities, may also have reservations around discussing sex. Some older heterosexual individuals may misperceive HIV/AIDS as merely a "gay disease" that does not affect them. Since preventing pregnancy is usually not a concern in couples over 50 they are less likely to use barrier methods (condoms). Discussions between physicians and older patients around risk reduction and safe sex practices can be challenging for many of these reasons. Targeted HIV prevention education for those at risk, and the integration of sexual health into the promotion of general well-being, however, can be invaluable.[9] Counseling is especially relevant for men being treated for erectile dysfunction as higher rates of sexually transmitted diseases and HIV infection occur in this group.[36]

Finally, although pre-exposure prophylaxis with daily tenofovir disoproxil fumarate plus emtricitabine has been shown to be highly effective in preventing HIV infection among adherent, high risk-younger patients, the balance between risks and benefits of this intervention are less favorable among older patients with increased co-morbidities.[37]

Conclusion

The increasing survival into old age of those infected with HIV reflects an extraordinary achievement in modern medicine. However, the benefits of treatment can only be reaped by HIV-infected patients who made aware of their condition through diagnostic testing and who are linked to and retained in care for their condition.

The poor survival and high rates of AIDS when HIV is diagnosed among older individuals is in large part the result of inadequate screening and the under-recognition of those with disease. Both the CDC and USPSTF recommend routine screening at least once-per-lifetime

for individuals up to age 64, regardless of risk factors, and annually for those who are at significant risk, whereas the American College of Physicians recommends testing up to age 75 for persons who might transmit HIV to others.

Once diagnosed, ART is strongly recommended for all patients regardless of CD4+ cell count or age.[10;12] While recommended for all patients regardless of age, early initiation of therapy is especially important for older patients as they are less likely to recover immunologic function after CD4+ cell loss. Lower CD4+ counts and viral replication not only places older patients at increased risk not for HIV-related complications but also for a myriad of co-morbidities including non-AIDS defining malignancies, cardiovascular disease and neurological disorders.

The management of HIV infection in older patients requires careful monitoring for bone, kidney, metabolic, cardiovascular, and liver health as well as careful attention to issues related to polypharmacy (e.g., drug-drug interactions and adverse effects) and the global care of an increasingly frail population that often suffers from stigma and limited social support. The impact of non-AIDS events underscores the importance of clinicians focusing on modifiable risk factors considered in traditional primary care in addition to optimizing HIV therapy. As the HIV patient population ages, the skills of geriatricians will increasingly be needed to manage these complex patients with multiple morbid conditions.

Table 1

Recommended Regimens for ART-naïve patients

Integrate Strand Transfer Inhibitor - Based Regimens:

- Dolutegravir/abacavir/lamivudine (given as the fixed combination pill Triumeq™) – **only** for patients who are HLA-B*5701 negative
- Dolutegravir plus tenofovir disoproxil fumarate (TDF)/emtricitabine (given as the fixed combination pill Truvada™)
- Elvitegravir/cobicistat/TDF/emtricitabine (given as the fixed combination pill Stribild™) – **only** for patients with pre-ART CrCl >70 mL/min
- Raltegravir (RAL) plus TDF/emtricitabine (given as the fixed combination pill Truvada™)

Protease Inhibitor - Based Regimens:

- Darunavir/ritonavir plus TDF/emtricitabine

For more detailed recommendations, readers are encouraged to refer to the most up-to-date DHHS guideline (http://aidsinfo.nih.gov/guidelines).

Table 2

Common Adverse Effects of Frequently Used Antiretroviral Agents

Agent	Associated Potential Adverse Effects*
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
All NRTIs	Lactic acidosis and hepatic steatosis (rare but high mortality, highest incidence with stavudine, didanosine and to a lesser extent zidovudine) Lipodystrophy (mostly with stavudine and zidovudine)
Abacavir	Hypersensitivity (in patients positive for HLA-B*5701) Possible increased risk of MI
Emtricitabine, lamivudine	In persons co-infected with Hepatitis B virus HBV coinfection, exacerbation of hepatitis if discontinued
Tenofovir disoproxil fumarate	Renal impairment (concurrent PI use may increase risk) Decrease in bone mineral density In persons co-infected with Hepatitis B virus HBV coinfection, exacerbation of hepatitis if discontinued Headache, gastrointestinal intolerance
Zidovudine	Bone marrow suppression Hyperlipidemia Insulin resistance Headache, gastrointestinal intolerance Myopathy
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
All NNRTIs	Rash (including Stevens-Johnson syndrome) Hepatotoxicity (especially NVP) Drug-drug interactions
Efavirenz	Neuropsychiatric Sleep disturbance Hyperlipidemia
Rilpivirine	Depression Insomnia Headache

Table 2 (continued)

Common Adverse Effects of Frequently Used Antiretroviral Agents

Agent	Associated Potential Adverse Effects*
Protease Inhibitors (PIs)	
All PIs	Hyperlipidemia Lipodystrophy Hepatotoxicity Gastrointestinal intolerance Drug-drug interactions
Atazanavir	Hyperbilirubinemia PR prolongation Nephrolithiasis, cholelithiasis Renal insufficiency
Darunavir	Rash Hepatotoxicity
Lopinavir/ritonavir	Gastrointestinal intolerance Diabetes/insulin resistance Possible increased risk of MI PR and QT prolongation
Integrate Strand Transfer Inhibitors (INSTIs)	
All INSTIs	Minimal toxicity and generally well-tolerated
Dolutegravir	Headache Insomnia Rash, hypersensitivity
Elvitegravir	Nausea, diarrhea
Raltegravir	Rash, Hypersensitivity Nausea Headache Diarrhea CPK elevation, myopathy, rhabdomyolysis
Other	
Cobicstat and ritonavir	Drug-drug interactions Increased serum creatinine (cobicistat) GI intolerance and hepatitis (ritonavir)

*This list includes key toxicities for the most commonly used anti-retroviral agents but is not all-inclusive. An additional comprehensive list of drug interactions can be found at http://www.hiv-druginteractions.org/. Further information about drug adverse effects are available within the DHHS guidelines[10]

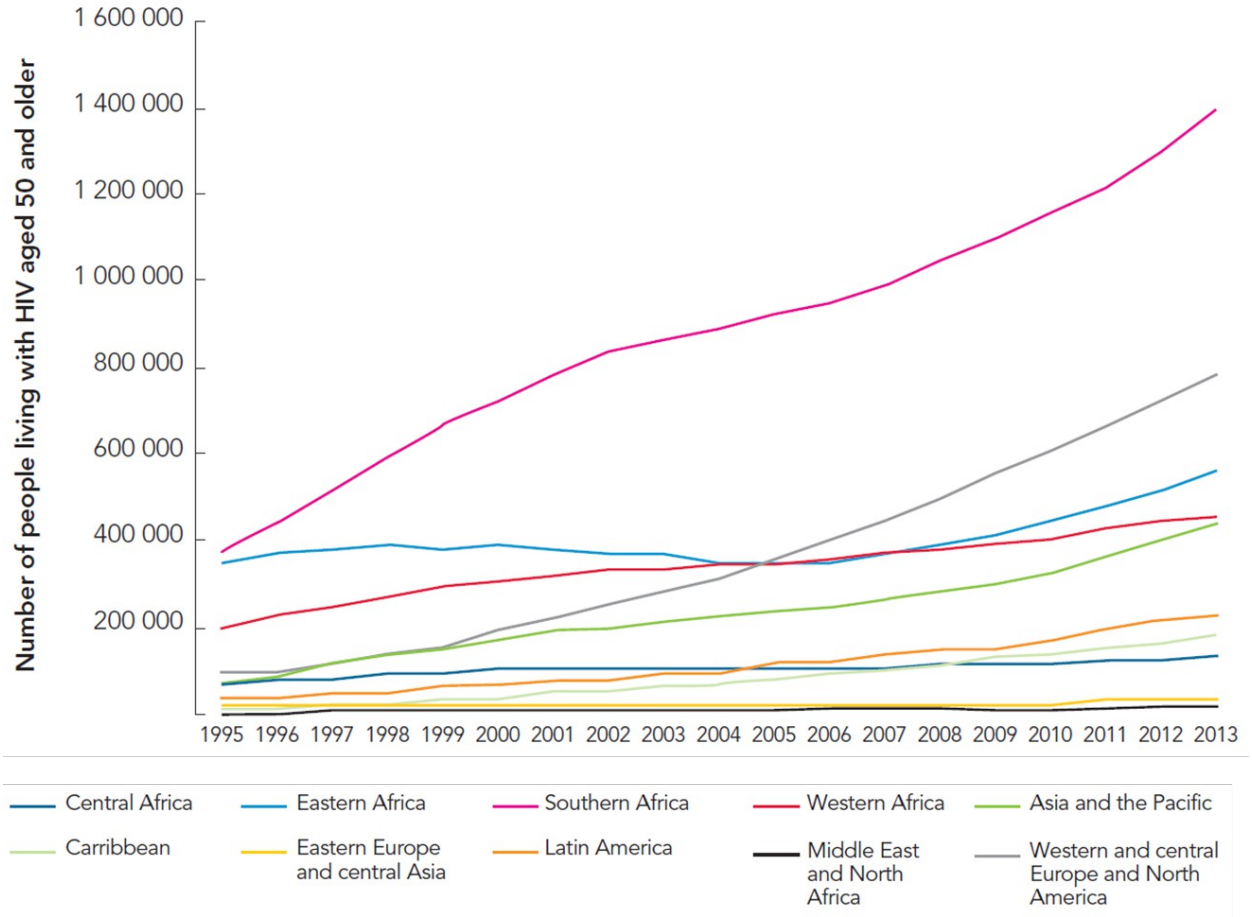
Figure Legends

Figure 1: Estimated number of people living with HIV aged 50 and older by region, 1995–2013

Figure 2: Clinical Status at Time of Diagnosis USA – 2013. Bars show the number of cases in each age strata who at the time of diagnosis of HIV infection who did (black bar) or did not (gray bar) have an AIDS-defining diagnosis. The dotted line shows the percentage of patients who had an AIDS-defining diagnosis. Data are from CDC HIV Surveillance Report, 2013; vol. 25.[2]

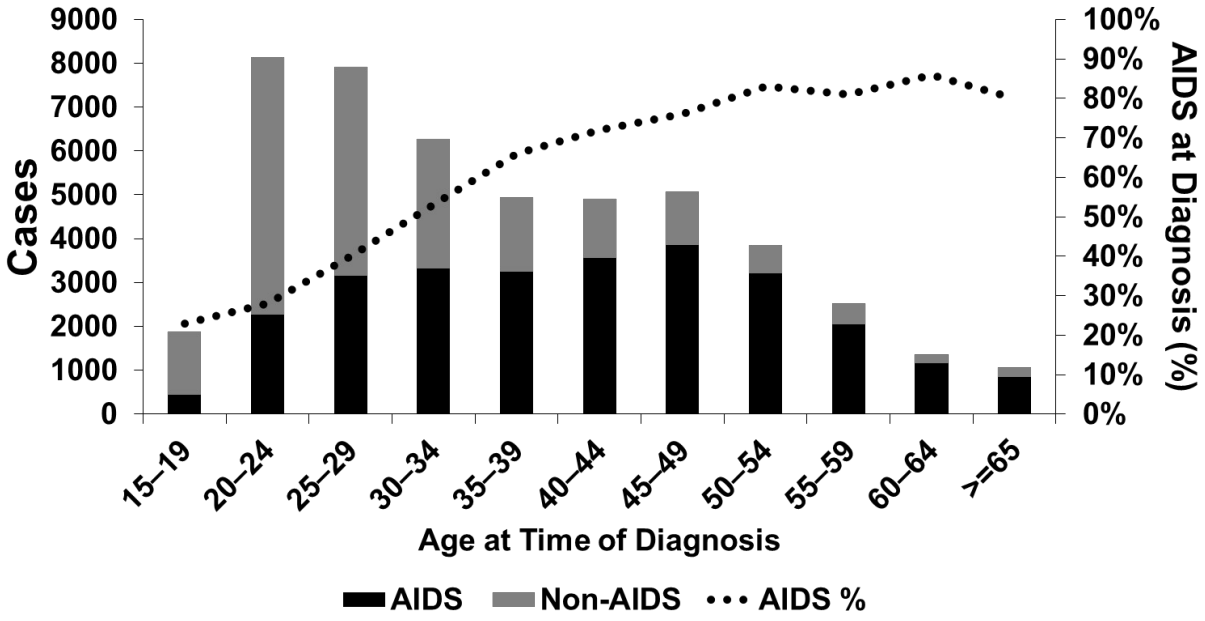
Figure 3: Mortality after Diagnosis of HIV Infection USA 2004 - 2009. Bars show the mortality rate at 1 (black bar), 2 (horizontal dashes) and 3 (gray bar) years after a diagnosis of HIV infection stratified by age. Data are from CDC HIV Surveillance Report, 2013; vol. 25.[2]

Figure 1



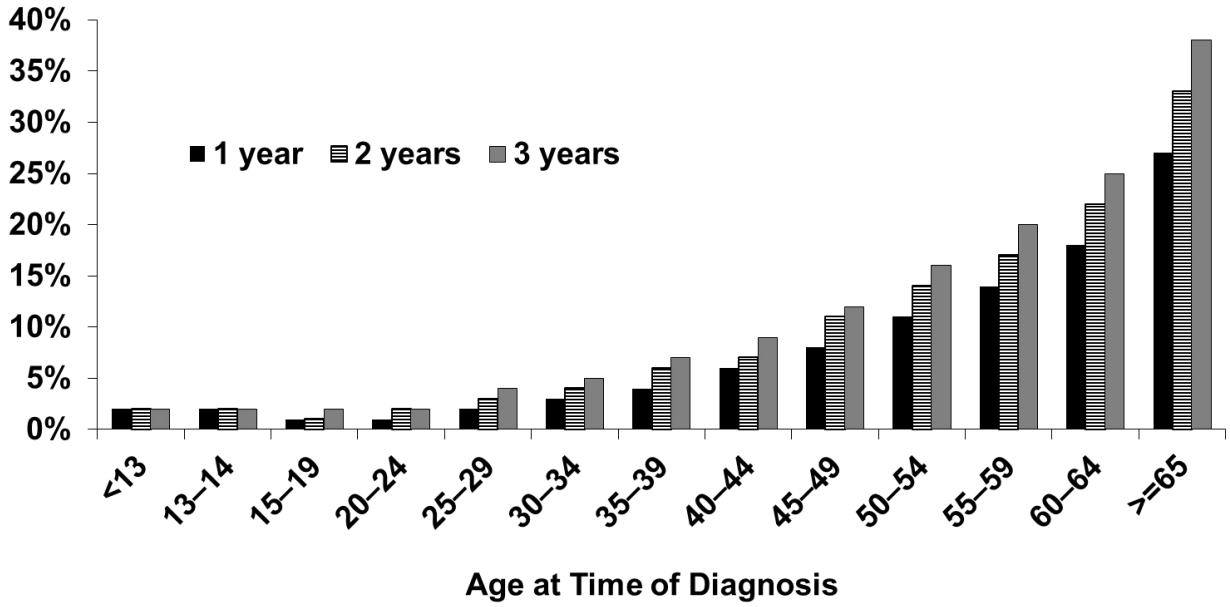
Source: UNAIDS 2013 estimates[3]

Figure 2



Data from CDC HIV Surveillance Report, 2013; vol. 25.[2]

Figure 3



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