



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

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 7/1/2013

Visit the *AIDSinfo* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

Initiating Antiretroviral Therapy in Treatment-Naive Patients (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression. The strength and evidence for this recommendation vary by pretreatment CD4 cell count: CD4 count <350 cells/mm³ (**A1**); CD4 count 350–500 cells/mm³ (**AII**); CD4 count >500 cells/mm³ (**BIII**).
- ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV. The strength and evidence for this recommendation vary by transmission risks: perinatal transmission (**A1**); heterosexual transmission (**A1**); other transmission risk groups (**AIII**).
- Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence (**AIII**). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Introduction

Without treatment, the vast majority of HIV-infected individuals will eventually develop progressive immunosuppression (as evident by CD4 count depletion), leading to AIDS-defining illnesses and premature death. The primary goal of antiretroviral therapy (ART) is to prevent HIV-associated morbidity and mortality. This goal is best accomplished by using effective ART to maximally inhibit HIV replication so that plasma HIV RNA levels (viral load) remain below that detectable by commercially available assays. Durable viral suppression improves immune function and quality of life, lowers the risk of both AIDS-defining and non-AIDS-defining complications, and prolongs life.

Furthermore, high plasma HIV RNA is a major risk factor for HIV transmission and use of effective ART can reduce viremia and transmission of HIV to sexual partners.^{1,2} Modelling studies suggest that the expanded use of ART may result in lower incidence and, eventually, prevalence of HIV on a community or population level.³ Thus, a secondary goal of ART is to reduce the risk of HIV transmission.

Historically, HIV-infected individuals have presented for care with low CD4 counts,⁴ but increasingly there have been concerted efforts to both increase testing of at-risk patients and to link HIV-infected patients to medical care soon after HIV diagnosis (and before they have advanced HIV diseases). For those with high CD4 cell counts, whose short-term risk for death may be low,⁵ the recommendation to initiate ART is based on growing evidence that untreated HIV infection or uncontrolled viremia is associated with development of non-AIDS-defining diseases, including cardiovascular disease (CVD), kidney disease, liver disease, neurologic complications, and malignancies. Furthermore, newer ART regimens are more effective, more convenient, and better tolerated than regimens used in the past.

Regardless of CD4 count, the decision to initiate ART should always include consideration of any co-morbid conditions, the willingness and readiness of the patient to initiate therapy, and the availability of resources. In settings where resources are not available to initiate ART in all patients, treatment should be prioritized for patients with the lowest CD4 counts and those with the following clinical conditions: pregnancy, CD4 count <200 cells/mm³, or history of an AIDS-defining illness, including HIV-associated dementia, HIV-associated nephropathy (HIVAN), hepatitis B virus (HBV), and acute HIV infection.

Tempering the enthusiasm to treat all patients regardless of CD4 count is the absence of randomized data that definitively demonstrate a clear clinical benefit of ART in patients with CD4 count >350 cells/mm³ and mixed results from observational cohort studies on the definitive benefits of early ART. For some patients, the potential risks of short- or long-term, drug-related complications and non-adherence to long-term therapy in asymptomatic patients may offset possible benefits of earlier initiation of therapy. An ongoing randomized controlled trial to evaluate the role of immediate versus delayed ART in patients with CD4 count >500 cells/mm³ will help to further define the role of ART in this patient population (ClinicalTrials.gov identifier NCT00867048).

The known and potential benefits and limitations of ART overall, and in different patient populations are discussed below.

Benefits of Antiretroviral Therapy

Reduction in Mortality and/or AIDS-Related Morbidity According to Pretreatment CD4 Cell Count

Patients with a history of an AIDS-defining illness or CD4 count <350 cells/mm³

HIV-infected patients with CD4 counts <200 cells/mm³ are at higher risk of opportunistic diseases, non-AIDS morbidity, and death than HIV-infected patients with higher CD4 counts. Randomized controlled trials in patients with CD4 counts <200 cells/mm³ and/or a history of an AIDS-defining condition provide strong evidence that ART improves survival and delays disease progression in these patients.⁶⁻⁸ Long-term data from multiple observational cohort studies comparing earlier ART (i.e., initiated at CD4 count >200 cells/mm³) with later treatment (i.e., initiated at CD4 count <200 cells/mm³) also have provided strong support for these findings.⁹⁻¹⁴

Few large, randomized controlled trials address when to start therapy in patients with CD4 counts >200 cells/mm³. CIPRA HT-001, a randomized clinical trial conducted in Haiti, enrolled 816 participants without AIDS. Participants were randomized to start ART with CD4 counts of 200 cells/mm³ to 350 cells/mm³ or to defer treatment until their CD4 counts dropped to <200 cells/mm³ or they developed an AIDS-defining condition. An interim analysis of the study showed that, when compared with participants who began ART with CD4 counts of 200 cells/mm³ to 350 cells/mm³, patients who deferred therapy had a higher mortality rate (23 versus 6 deaths; hazard ratio [HR] = 4.0; 95% confidence interval [CI]: 1.6–9.8) and a higher rate of incident tuberculosis (TB) (HR = 2.0, 95% CI: 1.2–3.6).¹⁵

Collectively, these studies support the Panel's recommendation that ART should be initiated in patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm³ (**AI**).

Patients with CD4 counts between 350 and 500 cells/mm³

Data supporting initiation of ART in patients with CD4 counts ranging from 350 cells/mm³ to 500 cells/mm³ are derived from large observational studies and secondary analysis of randomized controlled trials. Analysis of the findings from the observational studies involved use of advanced statistical methods that minimize the bias and confounding that arise when observational data are used to address the question of when to start ART. However, unmeasured confounders for which adjustment was not possible may have influenced the analysis.

The ART Cohort Collaboration (ART-CC) included 45,691 patients from 18 cohort studies conducted primarily in North America and Europe. Data from ART-CC showed that the rate of progression to AIDS and/or death was higher when therapy was deferred until a patient's CD4 count fell to the 251 cells/mm³ to 350 cells/mm³ range than when ART was initiated at the 351 cells/mm³ to 450 cells/mm³ range (risk ratio: 1.28, 95% CI: 1.04–1.57).¹¹ When analysis of the data was restricted to mortality alone, the difference between the 2 strategies was weaker and not statistically significant (risk ratio: 1.13, 95% CI: 0.80–1.60).

In a collaboration of North American cohort studies (NA-ACCORD) that evaluated patients regardless of whether they had started therapy, the 6,278 patients who deferred therapy until their CD4 counts were <350 cells/mm³ had greater risk of death than the 2,084 patients who initiated therapy with CD4 counts between 351 cells/mm³ and 500 cells/mm³ (risk ratio: 1.69, 95% CI: 1.26–2.26) after adjustment for other factors that differed between these 2 groups.¹⁶

Another collaboration of cohort studies from Europe and the United States (the HIV-CAUSAL Collaboration) included 8,392 ART-naive patients with initial CD4 counts >500 cells/mm³ who experienced declines in CD4 count to <500 cells/mm³.¹⁴ The study estimated that delaying initiation of ART until CD4 count <350 cells/mm³ was associated with a greater risk of AIDS-defining illness or death than initiating ART with CD4 count between 350 cells/mm³ and 500 cells/mm³ (HR: 1.38, 95% CI: 1.23–1.56). There was, however, no evidence of a difference in mortality (HR: 1.01, 95% CI: 0.84–1.22).

A collaboration of cohort studies from Europe, Australia, and Canada (the CASCADE Collaboration) included 5,527 ART-naive patients with CD4 counts in the 350 to 499 cells/mm³ range. Compared with patients who deferred therapy until their CD4 counts fell to <350 cells/mm³, patients who started ART immediately had a marginally lower risk of AIDS-defining illness or death (HR: 0.75, 95% CI: 0.49–1.14) and a lower risk of death (HR: 0.51, 95% CI: 0.33–0.80).¹⁷

Randomized data showing clinical evidence favoring ART in patients with higher CD4 cell counts came from two studies. First, in a small subgroup analysis of the SMART trial, undertaken primarily in North and South America, Europe, and Australia, which randomized participants with CD4 counts >350 cells/mm³ to continuous ART or to treatment interruption until CD4 count dropped to <250 cells/mm³. In the subgroup of 249 participants who were ART naive at enrollment (median CD4 count: 437 cells/mm³), participants who deferred therapy until CD4 count dropped to <250 cells/mm³ had a greater risk of serious AIDS- and non-AIDS-related events than those who initiated therapy immediately (7 vs. 2 events, HR: 4.6, 95% CI: 1.0–22.2).¹⁸

Second, the HPTN 052 was a large multinational, multicontinental (Africa, Asia, South America, and North America) randomized trial that examined whether treatment of HIV-infected individuals reduces transmission to their uninfected sexual partners.² A secondary objective of the study was to determine whether ART reduces clinical events in the HIV-infected participants. This trial enrolled 1,763 HIV-infected participants with CD4 counts between 350 cells/mm³ and 550 cells/mm³ and their HIV-uninfected partners. The infected participants were randomized to initiate ART immediately or to delay initiation until they had 2 consecutive CD4 counts <250 cells/mm³. At a median follow-up of 2.1 years, there were 77 primary events in the delayed arm versus 57 in the immediate therapy arm (adjusted HR: 1.39, 95% CI: 0.98–1.96). The most frequent event was tuberculosis (34 cases in the delayed therapy arm versus 17 in the immediate therapy arm); deaths were relatively rare (15 cases in the delayed therapy arm; 11 in the immediate therapy arm).¹⁹

Collectively, these studies suggest that initiating ART in patients with CD4 counts between 350 cells/mm³ and 500 cells/mm³ reduces HIV-related disease progression; whether there is a corresponding reduction in mortality is unclear. This benefit supports the Panel's recommendation that ART should be initiated in patients with CD4 counts 350 cells/mm³ to 500 cells/mm³ (AII). Recent evidence demonstrating the public health benefit of earlier intervention further supports the strength of this recommendation (see [Prevention of Sexual Transmission](#)).

Patients with CD4 counts >500 cells/mm³

The NA-ACCORD study also observed patients who started ART with CD4 counts >500 cells/mm³ or after their CD4 counts dropped below this threshold. The adjusted mortality rates were significantly higher in the 6,935 patients who deferred therapy until their CD4 counts fell to <500 cells/mm³ than in the 2,200 patients who started therapy with CD4 counts >500 cells/mm³ (risk ratio: 1.94, 95% CI: 1.37–2.79).¹⁶ Although large and generally representative of the HIV-infected patients in care in the United States, the study has several

limitations, including the small number of deaths and the potential for unmeasured confounders that might have influenced outcomes independent of ART.

In contrast, results from 2 cohort studies did not identify a benefit of earlier initiation of therapy in reducing AIDS progression or death. In an analysis of the ART-CC cohort,¹¹ the rate of progression to AIDS/death associated with deferral of therapy until CD4 count is in the 351 to 450 cells/mm³ range was similar to the rate with initiation of therapy with CD4 count in the 451 to 550 cells/mm³ range (HR: 0.99, 95% CI: 0.76–1.29). There was no significant difference in rate of death identified between the two groups (HR: 0.93, 95% CI: 0.60–1.44). This study also found that the proportion of patients with CD4 counts between 451 and 550 cells/mm³ who would progress to AIDS or death before having a CD4 count <450 cells/mm³ was low (1.6%; 95% CI: 1.1%–2.1%). In the CASCADE Collaboration,¹⁷ among the 5,162 patients with CD4 counts in the 500 to 799 cells/mm³ range, compared with patients who deferred therapy, those who started ART immediately did not experience a significant reduction in the composite outcome of progression to AIDS/death (HR: 1.10, 95% CI: 0.67–1.79) or death (HR: 1.02, 95% CI: 0.49–2.12).

While it was not a clinical endpoint study, a recent clinical trial (Setpoint Study) randomized patients within 6 months of HIV seroconversion to receive either immediate ART for 36 weeks or deferred treatment. More than 57% of the study participants had CD4 count >500 cells/mm³. The deferred treatment group had a statistically higher risk of meeting ART eligibility criteria than the immediate treatment group. The study was halted early and illustrated that the time from diagnosis of early infection to the need for initiation of ART was shorter than anticipated in the deferred therapy group.²⁰

The expanded use of ART to treat individuals with CD4 counts >500 cells/mm³ has also demonstrated public health benefits. In 2010, a large, publicly-funded clinic in San Francisco adapted a universal ART approach to initiate ART in all HIV-infected persons and evaluated temporal trends in viral suppression. In 534 patients entering the clinic with CD4 counts >500 cells/mm³, the 1-year incidence of viral suppression increased from 9% to 14% before universal ART to >52% after the approach was adopted. After adjustment, this policy was associated with a six-fold increase in the probability of viral suppression six months after clinic entry.²¹ Because the risk of HIV transmission is associated with level of viremia, from a public health standpoint, this reduction in community viral load can potentially reduce new HIV infections at the community level.

With a better understanding of the pathogenesis of HIV infection, the growing awareness that untreated HIV infection increases the risk of many non-AIDS-defining diseases (as discussed below), and the benefit of ART in reducing transmission of HIV, the Panel recommends initiation of ART in patients with CD4 counts >500 cells/mm³ (**BIII**).

When discussing initiation of ART at high CD4 cell counts (i.e., >500 cells/mm³), clinicians should inform patients that data on the clinical benefit of starting treatment at such levels are not conclusive, especially for patients with very high CD4 counts. Clinicians should also inform patients that viral suppression from effective ART can reduce the risk of sexual transmission to others. Patients should also be told that untreated HIV infection will eventually lead to immunological deterioration and increased risk of clinical disease and death. Therefore, if therapy is not initiated, continued monitoring and close follow-up is necessary.

Further ongoing research (both randomized clinical trials and cohort studies) to assess the short- and long-term clinical and public health benefits and cost effectiveness of starting therapy at higher CD4 counts is needed. Findings from such research will provide the Panel with guidance to make future recommendations.

Effects of Viral Replication on HIV-Related Morbidity

Since the mid-1990s, it has been known that measures of viral replication are predictive of HIV disease progression. In untreated HIV-infected individuals, time to clinical progression and mortality is fastest in those with higher viral loads.²² This finding is confirmed across the wide spectrum of HIV-infected patient

populations, including injection drug users (IDUs),²³ women,²⁴ and individuals with hemophilia.²⁵ Several studies have shown the prognostic value of pre-treatment viral load for predicting post-therapy response.^{26,27} Once therapy has been initiated, failure to achieve viral suppression²⁸⁻³⁰ and viral load at the time of treatment failure³¹ are predictive of clinical disease progression.

More recent studies have examined the impact of ongoing viral replication for both longer durations and at higher CD4 cell counts. Using viremia copy-years, a novel metric for quantifying viral load over time, the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort found that cumulative exposure to replicating virus is independently associated with mortality. Using viremia copy-years, the HR for mortality was 1.81 per log₁₀ copy-year/mL (95% CI: 1.51–2.18), which was the only viral load-related variable that retained statistical significance in the multivariable model (HR 1.44 per log₁₀ copy-year/mL; 95% CI: 1.07–1.94). These findings support the concept that unchecked viral replication, which occurs in the absence of effective ART, is a factor in disease progression and death independent of CD4 count.³²

The EuroSIDA collaboration evaluated HIV-infected individuals with CD4 counts >350 cells/mm³ segregated by three viral load strata (<500 copies/mL, 500–9,999 copies/mL, and ≥10,000 copies/mL) to determine the impact of viral load on fatal and non-fatal AIDS-related and non-AIDS-related events. The lower viral load stratum included more subjects on ART (92%) than the middle (62%) and high (31%) viral load strata. After adjustment for age, region, and ART, the rates of non-AIDS events were 61% (*P* = 0.001) and 66% (*P* = 0.004) higher in participants with viral loads 500 to 9,999 copies/mL and >10,000 copies/mL, respectively, than in individuals with viral loads <500 copies/mL. These data further confirm that unchecked viral replication is associated with adverse clinical outcomes in individuals with CD4 counts >350 cells/mm³.³³

Collectively, these data show that the harm of ongoing viral replication affects both untreated patients and those who are on ART but continue to be viremic. The harm of ongoing viral replication in patients on ART is compounded by the risk of emergence of drug-resistant virus. Therefore, all patients on ART should be carefully monitored and counseled on the importance of adherence to therapy.

Effects of ART on HIV-Related Morbidity

HIV-associated immune deficiency, the direct effects of HIV on end organs, and the indirect effects of HIV-associated inflammation on these organs all most likely contribute to HIV-related morbidity and mortality. In general, the available data demonstrate that

- Untreated HIV infection may have detrimental effects at all stages of infection,
- Earlier treatment may prevent the damage associated with HIV replication during early stages of infection,
- ART is beneficial even when initiated later in infection; however, later therapy may not repair damage associated with viral replication that occurred during early stages of infection, and
- Sustaining viral suppression and maintaining higher CD4 count, mostly as a result of effective combination ART, may delay, prevent, or reverse some non-AIDS-defining complications, such as HIV-associated kidney disease, liver disease, CVD, neurologic complications, and malignancies, as discussed below.

HIV-associated nephropathy (HIVAN)

HIVAN is the most common cause of chronic kidney disease in HIV-infected individuals that may lead to end-stage kidney disease.³⁴ HIVAN is almost exclusively seen in black patients and can occur at any CD4 count. Ongoing viral replication appears to be directly involved in renal injury,³⁵ and HIVAN is extremely uncommon in virologically suppressed patients.³⁶ ART in patients with HIVAN has been associated with both

preserved renal function and prolonged survival.³⁷⁻³⁹ Therefore, ART should be started in all patients with HIVAN, regardless of CD4 count, at the earliest sign of renal dysfunction (**AII**).

Coinfection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV)

HIV infection is associated with more rapid progression of viral hepatitis-related liver disease, including cirrhosis, end-stage liver disease, hepatocellular carcinoma, and fatal hepatic failure.⁴⁰⁻⁴² The pathogenesis of accelerated liver disease in HIV-infected patients has not been fully elucidated, but HIV-related immunodeficiency and a direct interaction between HIV and hepatic stellate and Kupffer cells have been implicated.⁴³⁻⁴⁶ In individuals co-infected with hepatitis B virus (HBV) and/or hepatitis C virus (HCV), ART may attenuate liver disease progression by preserving or restoring immune function and reducing HIV-related immune activation and inflammation.⁴⁷⁻⁴⁹ ARV drugs active against both HIV and HBV (such as tenofovir disoproxil fumarate [TDF], lamivudine [3TC], and emtricitabine [FTC]) also may prevent development of significant liver disease by directly suppressing HBV replication.^{50, 51} Although ARV drugs do not inhibit HCV replication directly, HCV treatment outcomes typically improve when HIV replication is controlled or CD4 counts are increased.⁵² **In one prospective cohort, after controlling for liver and HIV disease stage, HCV co-infected patients receiving ART were approximately 66% less likely to experience end-stage liver disease, hepatocellular carcinoma, and fatal hepatic failure than patients not receiving ART.**⁵³

While some studies have shown that chronic viral hepatitis increases the risk of ART-induced liver injury, the majority of coinfecting persons do not develop clinically significant liver injury⁵⁴⁻⁵⁶ and the rate of hepatotoxicity may be greater in persons with more advanced HIV disease. Collectively, these data suggest that earlier treatment of HIV infection in persons coinfecting with HBV (and likely HCV) may reduce the risk of liver disease progression. ART is recommended for patients coinfecting with HBV; the ART regimen should include drugs with activity against both HIV and HBV (**AII**) (also see [Hepatitis B Virus/HIV Co-Infection](#)). ART also is recommended for most patients coinfecting with HCV (**BII**), including those with high CD4 counts and those with cirrhosis. **This recommendation is based on findings from retrospective and prospective cohort studies that indicated that the receipt of ART is associated with slower progression of hepatic fibrosis and reduced risk of liver disease outcomes.**^{53, 57-59} Combined treatment of both HIV and HCV can be complicated by large pill burden, drug interactions, and overlapping toxicities. Although ART should be considered for HIV/HCV-co-infected patients regardless of CD4 cell count, for patients infected with HCV genotype 1, some clinicians may choose to defer ART in HIV treatment-naïve patients with CD4 counts >500 cells/mm³ until HCV treatment that includes the HCV NS3/4A protease inhibitors (PIs) is completed (also see [HIV/Hepatitis C Virus Co-Infection](#)).

Cardiovascular disease (CVD)

In HIV-infected patients, CVD is a major cause of morbidity and mortality, accounting for one-third of serious non-AIDS conditions and at least 10% of deaths.⁶⁰⁻⁶² **A number of studies have found that, over time, HIV-infected persons are at greater risk for CVD events than age-matched uninfected individuals. In a meta-analysis and review of studies of CVD risk in HIV-infected individuals, the relative risk of CVD events was greater in untreated HIV-infected patients than in HIV-uninfected individuals (1.61: 95% CI 1.43 to 1.81).**⁶³ It is important to note, however, that the selected studies made comparisons to the general population, did not control for smoking or other potential confounders that could lead to excessive CVD in the HIV-infected individuals, and also did not attempt to account for competing risks.⁶⁴ Thus, questions remain regarding the relative contributions of host-, treatment-, and disease-related factors to excess number of CVD events in those with HIV infection.

Persons living with HIV infection have higher rates of established CVD risk factors, particularly smoking and dyslipidemia than HIV-uninfected individuals. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort study such factors, including age; male gender; obesity; smoking; family history of CVD; diabetes; and dyslipidemia, were each strongly and independently associated with risk of myocardial

infarction (MI).⁶⁵ This study also found that the risk of CVD was greater with exposure to some ARV drugs, including certain PIs and abacavir, than with exposure to other ARV drugs.^{65, 66}

In terms of preventing the progression to CVD events, it has not been determined whether delaying ART initiation is preferable to immediate treatment. **In the meta-analysis mentioned above, the risk of CVD in HIV-infected individuals was 1.5 times higher in those being treated with ART than in those not being treated with ART.**⁶³ These analyses were limited by concern that the treated individuals may have been infected for longer periods of time and had prior episodes of untreated HIV disease, as well as the fact that **the untreated people were at higher risk for competing events, including death.** Furthermore, there is evidence that untreated HIV infection also may be associated with an increased risk of CVD. In the SMART study, the risk of cardiovascular events was greater in participants randomized to CD4-guided treatment interruption than in participants who received continuous ART.⁶⁷ In other studies, ART resulted in marked improvement in parameters associated with CVD, including markers of inflammation (such as interleukin 6 [IL-6]), immune dysfunction (e.g., T cell activation, T cell senescence), monocyte activation (e.g., IL-6, CD163), hypercoagulation (e.g., D-dimers) and, most importantly, endothelial dysfunction.^{68, 69} Low nadir and/or proximal on-therapy CD4 cell count has been linked to CVD (MI and/or stroke),⁷⁰⁻⁷² suggesting that low CD4 count might result in increased risk of CVD.

Collectively, the increased risk of cardiovascular events with treatment interruption, the effects of ART on markers of inflammation and endothelial dysfunction, and the association between CVD and CD4 cell depletion suggest that early control of HIV replication with ART can be used as a strategy to reduce risk of CVD, particularly if drugs with potential cardiovascular toxicity are avoided. However, at this time no study has demonstrated that initiation of ART prevents CVD. Therefore, a role for early ART in preventing CVD remains to be established. For HIV-infected individuals with a significant risk of CVD, as assessed by medical history and established estimated risk calculations, risk of CVD should be taken into consideration when selecting a specific ART regimen.

Malignancies

Population-based analyses suggest that the incidence of both AIDS-defining malignancies (i.e., Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) and non-AIDS-defining malignancies is increased in chronic HIV infection. **The incidence of several malignancies (particularly liver, anal, oropharyngeal, and lung cancers, Hodgkin lymphoma, and melanoma) is higher in HIV-infected subjects than in matched HIV-uninfected controls,**^{73, 74} and the burden of these non-AIDS defining malignancies has continued to increase in the United States between 1996 and 2007.⁷⁵ Large cohort studies enrolling mainly patients receiving ART have reported a consistent link between low CD4 counts (<350 cells/mm³ to 500 cells/mm³) and the risk of AIDS- and/or non-AIDS-defining malignancies.^{12, 72, 76-79} The ANRS C04 Study demonstrated a statistically significant relative risk of all cancers evaluated (except for anal carcinoma) in patients with CD4 counts <500 cells/mm³ compared with patients with current CD4 counts >500 cells/mm³, **an increased risk of anal cancer based on time with CD4 counts <200 cells/mm³,** and, regardless of CD4 count, a protective effect of ART for HIV-associated malignancies.⁷⁶ This potential effect of HIV-associated immunodeficiency is striking particularly with regard to cancers associated with chronic viral infections such as HBV, HCV, human papilloma virus (HPV), Epstein-Barr virus (EBV), and human herpes virus-8 (HHV-8).^{80, 81} Cumulative HIV viremia, independent of other factors, may also be associated with the risk of non-Hodgkin lymphoma and other AIDS-defining malignancies.^{79, 82} From the early 1990s through 2000, incidence rates for many cancers, including Kaposi sarcoma, diffuse large B-cell lymphoma, and primary central nervous system (CNS) lymphoma, declined markedly in HIV-infected individuals in the United States, with more gradual declines noted after 2000.⁸³ However, for other AIDS-defining and non-AIDS defining cancers, such as Burkitt lymphoma, Hodgkin lymphoma, cervical cancer, and anal cancer, similar reductions in incidence have not been observed.^{83, 84} Declines in overall mortality and aging of HIV-infected cohorts increase overall

cancer incidence, which may confound a clear assessment of the impact of ART on preventing the development of malignancies.^{75, 85} In the SMART study,⁸⁶ patients randomized to the drug conservation arm (i.e., those starting ART with CD4 count <250 cells/mm³) had a higher incidence of AIDS-defining malignancies, but not non-AIDS defining malignancies, than patients in the viral suppression arm (i.e., those receiving continuous ART). In a pooled analysis of the ESPRIT and SMART studies,⁸⁷ history of an AIDS-defining event increased risk of any cancer. Taken together this evidence suggests that initiating ART to suppress HIV replication and maintain CD4 counts at levels >350 to 500 cells/mm³ reduces the overall incidence of AIDS-defining malignancies and may also reduce the risk of non-AIDS-defining malignancies. The effect on incidence is most likely heterogeneous across various cancer types.

Neurological diseases

Although HIV RNA can be detected in the cerebrospinal fluid (CSF) of most untreated patients,^{88, 89} these patients usually do not present with overt symptoms of HIV-associated neurological disease.⁹⁰ In some patients, CNS infection progresses to HIV encephalitis and can present as HIV-associated dementia (HAD).⁹¹⁻⁹³ This progression is usually in the context of more advanced untreated systemic HIV infection when severe CNS opportunistic infections (OIs) also cause high morbidity and mortality.⁹⁴

Effective viral suppression resulting from ART has dramatically reduced the incidence of HAD and severe CNS OIs.⁹⁵⁻⁹⁷ Suppressive ART usually reduces CSF HIV RNA to undetectable levels.^{98, 99} Exceptional cases of symptomatic and asymptomatic CNS viral escape, in which HIV RNA is detectable in CSF despite viral suppression in plasma, have been documented.^{100, 101} This suggests that in some settings it may be useful to monitor CSF HIV RNA.

Recent attention has turned to milder forms of CNS dysfunction, defined by impairment on formal neuropsychological testing.^{93, 102} It is unclear whether this impairment is a consequence of injury sustained before treatment initiation or whether neurologic damage can continue or develop despite systemically effective ART.¹⁰³ The association between cognitive impairment and low nadir CD4 counts supports the hypothesis for pretreatment injury and bolsters the argument that earlier initiation of ART may prevent subsequent brain dysfunction.^{104, 105}

The peripheral nervous system (PNS) also is a target in HIV infection, and several types of neuropathies have been identified.¹⁰⁶ Most common is HIV-associated polyneuropathy, a chronic, predominantly sensory and sometimes painful neuropathy. The impact of early treatment on this and other forms of neuropathy is not as clearly defined as that on HAD.^{107, 108}

Age and treatment-related immune reconstitution (also see [HIV and the Older Patient](#))

The CD4 cell response to ART is an important predictor of short- and long-term morbidity and mortality. Treatment initiation at an older age is consistently associated with a less robust CD4 count response; starting therapy at a younger age may result in better immunologic and perhaps clinical outcomes.¹⁰⁹⁻¹¹²

T-cell activation and inflammation

Early untreated HIV infection is associated with sustained high-level inflammation and T-cell activation.¹¹³⁻¹¹⁵ The degree of T-cell activation during untreated HIV disease is associated with risk of subsequent disease progression, independent of other factors such as plasma HIV RNA levels and peripheral CD4 T-cell count.^{116, 117} ART results in a rapid, but often incomplete, decrease in most markers of HIV-associated immune activation.^{87, 118-121} Persistent T-cell activation and/or T-cell dysfunction is particularly evident in patients who delay therapy until later stage disease (CD4 count <350 cells/mm³).^{119, 121, 122} The degree of persistent inflammation during treatment, as represented by the levels of IL-6, D-dimers, sCD14, and sCD163, may be independently associated with risk of morbidity and mortality.¹²³⁻¹²⁵ Collectively, these observations support earlier use of ART for at least two reasons. First, treatment decreases the level of inflammation, which may be

associated with reduced short-term risk of AIDS- and non-AIDS-related morbidity and mortality.^{123, 126, 127} Second, because the degree of residual inflammation and/or T-cell dysfunction with ART appears to be higher in patients with lower CD4 cell nadirs,^{119, 121, 122} earlier treatment may result in less residual immunological perturbations on therapy and, hence, less risk for AIDS- and non-AIDS-related complications (**CIII**).

Antiretroviral Therapy for Prevention of HIV Transmission

Prevention of perinatal transmission

Effective ART reduces transmission of HIV. The most dramatic and well-established example of this effect is the use of ART in pregnant women to prevent perinatal transmission of HIV. Effective suppression of HIV replication, as reflected in plasma HIV RNA, is a key determinant in reducing perinatal transmission. In the setting of ART initiation before 28 weeks' gestation and an HIV RNA level <50 copies/mL near delivery, use of combination ART during pregnancy has reduced the rate of perinatal transmission of HIV from approximately 20% to 30% to <0.5%.¹²⁸ Thus, use of combination ART drug regimens is recommended for all HIV-infected pregnant women (**AI**). Following delivery, in the absence of breastfeeding, considerations regarding continuation of the ARV regimen for maternal therapeutic indications are the same as those regarding ART for other non-pregnant individuals. For detailed recommendations, see the [Perinatal Guidelines](#).¹²⁹

Prevention of sexual transmission

Recent study results provide strong support for the premise that treatment of the HIV-infected individual can significantly reduce sexual transmission of HIV. Lower plasma HIV RNA levels are associated with decreases in the concentration of the virus in genital secretions.^{130, 131} Studies of HIV-serodiscordant heterosexual couples have demonstrated a relationship between level of plasma viremia and risk of transmission of HIV: when plasma HIV RNA levels are lower, transmission events are less common.^{1, 132-135}

HPTN 052 was a multicontinental trial that enrolled 1,763 HIV-serodiscordant couples in which the HIV-infected partner was ART naive with CD4 count 350 cells/mm³ to 550 cells/mm³ at enrollment. The study compared immediate ART with delayed therapy (i.e., not started until CD4 count <250 cells/mm³) for the HIV-infected partner.² At study entry, 98% of the participants were in heterosexual monogamous relationships. All study participants were counseled on behavioral modification and condom use. Twenty-eight linked HIV transmission events were identified during the study period, but only 1 event occurred in the early therapy arm. This 96% reduction in transmission associated with early ART was statistically significant (HR 0.04, 95% CI: 0.01–0.27, *P* <0.001). These results show that early ART is more effective at preventing transmission of HIV than all other behavioral and biomedical prevention interventions studied to date, including condom use, male circumcision, vaginal microbicides, HIV vaccination, and pre-exposure prophylaxis. This study, as well as other observational studies and modeling analyses showing a decreased rate of HIV transmission in serodiscordant heterosexual couples following the introduction of ART, demonstrate that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted diseases (STDs) substantially reduces the risk of transmission of HIV.^{3, 134-138} HPTN 052 was conducted in heterosexual couples and not in populations at risk of transmission via homosexual exposure or needle sharing, but the prevention benefits of effective ART presumably apply to these populations as well. Therefore, the Panel recommends that ART be offered to patients who are at risk of transmitting HIV to sexual partners. (The strength of this recommendation varies according to mode of sexual transmission: **AI** for heterosexual transmission and **AIII** for male-to-male and other modes of sexual transmission.) Clinicians should discuss with patients the potential individual and public health benefits of therapy and the need for adherence to the prescribed regimen and counsel patients that ART is not a substitute for condom use and behavioral modification and that ART does not protect against other STDs (also see [Preventing Secondary Transmission of HIV](#)).

Concerns Regarding Earlier Initiation of Therapy

Despite increasing evidence for the benefits associated with earlier initiation of ART, three areas of concern have served as a rationale for deferral of HIV therapy:

ARV drug toxicities have an adverse affect on quality of life and adherence.

Earlier initiation of ART extends exposure to ARV agents by several years. The D:A:D study found an increased incidence of CVD associated with cumulative exposure to some drugs in the nucleoside reverse transcriptase inhibitor and PI drug classes.^{65, 139} In the SMART study, when compared with interruption or deferral of therapy, continuous exposure to ART was associated with significantly greater loss of bone density.⁶⁷ There may be unknown complications related to cumulative use of ARV drugs for many decades. A list of known ARV-associated toxicities can be found in [Adverse Effects of Antiretroviral Agents](#).

ART frequently improves quality of life for symptomatic patients. However, some side effects of ART may impair quality of life for some patients, especially those who are asymptomatic at initiation of therapy. For example, efavirenz (EFV) can cause neurocognitive or psychiatric side effects and PIs have been associated with gastrointestinal (GI) side effects. As noted above, it has been suggested that some therapies increase the risk of CVD. Some patients may find that the inconvenience of taking medication every day outweighs the overall benefit of early ART and may choose to delay therapy.

ARV non-adherence may have an impact on virologic efficacy.

At any CD4 count, adherence to therapy is essential to achieve viral suppression and prevent emergence of drug-resistance mutations. Several behavioral and social factors associated with poor adherence, such as untreated major psychiatric disorders, active substance abuse, unfavorable social circumstances, patient concerns about side effects, and poor adherence to clinic visits, have been identified. Clinicians should identify areas where additional intervention is needed to improve adherence both before and after initiation of therapy. Some strategies to improve adherence are discussed in [Adherence to Antiretroviral Therapy](#).

Earlier development of resistance may reduce therapeutic options at a later time.

Despite concerns about the development of resistance to ARV drugs, the evidence thus far indicates that resistance occurs more frequently in individuals who initiate therapy later in the course of infection than in those who initiate ART earlier.¹⁴⁰ Furthermore, recent data have indicated a slight increase in the prevalence of 2-drug class resistance from 2000 to 2005.¹⁴¹

Cost.

In resource-rich countries, the cost of ART exceeds \$10,000 per year (see [Appendix B, Table 8](#)). Several modeling studies support the cost effectiveness of HIV therapy initiated soon after diagnosis.¹⁴²⁻¹⁴⁴ One study reported that the annual cost of care is 2.5 times higher for patients with CD4 counts <50 cells/mm³ than for patients with CD4 counts >350 cells/mm³.¹⁴⁵ A large proportion of the health care expenditure in patients with advanced infection is from non-ARV drugs and hospitalization. There are no cost comparisons for patients starting ART with CD4 count 350 to 500 cells/mm³ and patients starting ART with CD4 count >500 cells/mm³.

Conditions Favoring More Rapid Initiation of Therapy

Several conditions increase the urgency for therapy, including:

- Pregnancy (AI) (Clinicians should refer to the [Perinatal Guidelines](#) for more detailed recommendations on the management of HIV-infected pregnant women.)¹²⁹
- AIDS-defining conditions, including HIV-associated dementia (AI)

- Acute opportunistic infections (OIs) (see discussion below)
- Lower CD4 counts (e.g., <200 cells/mm³) (**AI**)
- HIVAN (**AII**)
- Acute/recent infection (**BII**) (see more discussion in the [Acute and Recent \(Early\) Infection section](#))
- HIV/HBV coinfection (**AII**)
- HIV/HCV coinfection (**BII**)
- Rapidly declining CD4 counts (e.g., >100 cells/mm³ decrease per year) (**AIII**)
- Higher viral loads (e.g., >100,000 copies/mL) (**BII**)

Acute opportunistic infections

In patients with opportunistic conditions for which no effective therapy exists (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy) but in whom ART may improve outcomes by improving immune responses, the benefits of ART outweigh any increased risk; therefore, treatment should be started as soon as possible (**AIII**).

In the setting of some OIs for which immediate therapy may increase the risk of immune reconstitution inflammatory syndrome (IRIS) (e.g., cryptococcal meningitis or nontuberculous mycobacterial infections), a short delay before initiating ART may be warranted (**CIII**).^{146, 147} In the setting of other OIs, such as *Pneumocystis jiroveci* pneumonia (PCP), early initiation of ART is associated with increased survival;⁸ therefore, therapy should not be delayed (**AI**).

In patients who have active TB, initiating ART during treatment for TB confers a significant survival advantage,¹⁴⁸⁻¹⁵² therefore, ART should be initiated as recommended in [Mycobacterium Tuberculosis Disease with HIV Coinfection](#).

Clinicians should refer to the [Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents](#)¹⁵³ for more detailed discussion on when to initiate ART in the setting of a specific OI.

Conditions Where Deferral of Therapy May be Considered

Some patients and their clinicians may decide to defer therapy for a period of time on the basis of clinical or personal circumstances. Deferring therapy for the reasons discussed below may be reasonable in patients with high CD4 counts (e.g., >500 cells/mm³) but deferring therapy in patients with much lower CD4 counts (e.g., <200 cells/mm³) should be considered only in rare situations and should be undertaken with close clinical follow-up. Briefly delaying therapy to allow a patient more time to prepare for lifelong treatment may be considered.

When there are significant barriers to adherence (also see [Adherence to Antiretroviral Therapy](#))

In patients with higher CD4 counts who are at risk of poor adherence, it may be prudent to defer treatment while addressing the barriers to adherence. However, in patients with conditions that require urgent initiation of ART (see above), therapy should be started while simultaneously addressing the barriers to adherence.

Several methodologies exist to help providers assess adherence. When the most feasible measure of adherence is self-report, this assessment should be completed at each clinic visit using one of the available reliable and valid instruments.^{154, 155} If other objective measures (e.g., pharmacy refill data, pill count) are available, these methods should be used to assess adherence at each follow-up visit.¹⁵⁶⁻¹⁵⁸ Continuous assessment and counseling make it possible for the clinician to intervene early to address barriers to adherence occurring at any point during treatment (see [Adherence to Antiretroviral Therapy](#)).

Presence of comorbidities that complicate or prohibit antiretroviral therapy

Deferral of ART may be considered when either the treatment or manifestations of other medical conditions may complicate the treatment of HIV infection or vice versa. Examples include:

- Surgery that may result in an extended interruption of ART
- Treatment with medications that have clinically significant drug interactions with ART and for which alternative medications are not available

In each of these circumstances, the assumption is that the situation is temporary and that ART will be initiated after the conflicting condition has resolved.

Some less common situations exist in which ART may not be indicated at any time while CD4 counts remain high. In particular, such situations include that of patients with a poor prognosis due to a concomitant medical condition who would not be expected to gain survival or quality-of-life benefits from ART. Examples include patients with incurable non-HIV-related malignancies or end-stage liver disease who are not being considered for liver transplantation. The decision to forego ART in such patients may be easier to make in those with higher CD4 counts; they are likely asymptomatic for HIV, and their survival is unlikely to be prolonged by ART. However, it should be noted that ART may improve outcomes, including survival, in patients with some HIV-associated malignancies (e.g., lymphoma or Kaposi sarcoma) and in patients with liver disease due to chronic HBV or HCV.

Long-term nonprogressors and elite HIV controllers

A small subset of HIV-infected individuals (~3% to 5%) maintain normal CD4 counts for many years in the absence of therapy (long-term nonprogressors), and an even smaller subset (~1%) maintain undetectable HIV RNA level for years (“elite” controllers).^{159, 160} Many long-term non-progressors have detectable viremia while some elite controllers progress immunologically and/or clinically despite having no detectable viremia.

The evidence on how to manage these individuals is limited. Given the potential harm associated with uncontrolled HIV replication, many of the preceding arguments for early therapy most likely apply to non-progressors who have consistently detectable viremia (i.e., HIV RNA >200 to 1000 copies/mL). Also given that ongoing HIV replication occurs in elite controllers, ART is also recommended for those rare controllers who exhibit evidence of disease progression, as defined by declining CD4 counts or development of HIV-related complications. The Panel has no recommendations for the management of controllers with high CD4 counts, but the fact that these individuals have higher than normal levels of inflammation and immune activation provides at least some rationale for treatment. Clinical trials assessing the potential benefit of therapy in these individuals are ongoing.

The Need for Early Diagnosis of HIV

Fundamental to the earlier initiation of ART recommended in these guidelines is the assumption that patients will be diagnosed early in the course of HIV infection and linked to medical care, thereby, making earlier initiation of therapy an option. Unfortunately, most cases of HIV infection are not diagnosed until patients are at much later stages of disease,¹⁶¹⁻¹⁶⁴ although the mean CD4 count at initial presentation for care has increased in more recent years.⁴ Despite the 2006 Centers for Disease Control and Prevention (CDC) recommendations for routine, opt-out HIV screening in the health care setting regardless of perceptions about a patient’s risk of infection,¹⁶⁵ the median CD4 count of newly diagnosed patients remains below 350 cells/mm³.⁴ The exception is pregnant women whose infection was diagnosed during prenatal care; they have a much higher median initial CD4 count. Compared with other groups, diagnosis of HIV infection is more often delayed in nonwhites, IDUs, and older patients, and a substantial proportion of these individuals develop AIDS-defining illnesses within 1 year of diagnosis.¹⁶¹⁻¹⁶⁴ Thus, for the current treatment guidelines

to have maximum impact, routine HIV screening per current CDC recommendations is essential. It is also critical to educate all newly diagnosed patients about HIV disease and link them to care for full evaluation, follow-up, and management. Once patients are in care, focused effort is required to retain them in the health care system so that both infected individuals and their sexual partners can accrue the full benefits of early diagnosis and treatment.

Conclusion

The current recommendations are based on greater evidence supporting earlier initiation of ART than was advocated in previous guidelines. The strength of the recommendations varies according to the quality and availability of existing evidence supporting each recommendation. In addition to benefitting the health of the HIV-infected individual, the evidence that effective ART reduces sexual transmission to HIV provides further reason for earlier initiation of ART. The Panel will continue to monitor and assess the results of ongoing and planned randomized clinical trials and observational studies. Findings from these studies will provide the Panel with additional guidance to form future recommendations.

References

1. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. 2000;342(13):921-929. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10738050.
2. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21767103.
3. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009;373(9657):48-57. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19038438.
4. Althoff KN, Gange SJ, Klein MB, et al. Late presentation for human immunodeficiency virus care in the United States and Canada. *Clin Infect Dis*. 2010;50(11):1512-1520. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20415573>.
5. Study Group on Death Rates at High CDCiANP, Lodwick RK, Sabin CA, et al. Death rates in HIV-positive antiretroviral-naïve patients with CD4 count greater than 350 cells per microL in Europe and North America: a pooled cohort observational study. *Lancet*. 2010;376(9738):340-345. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20638118>.
6. HIV Trialists' Collaborative Group. Zidovudine, didanosine, and zalcitabine in the treatment of HIV infection: meta-analyses of the randomised evidence. *Lancet*. 1999;353(9169):2014-2025. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10376616.
7. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med*. 1997;337(11):725-733. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9287227.
8. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19440326.
9. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet*. 1998;352(9142):1725-1730. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9848347.

10. Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA*. 2001;286(20):2568-2577. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11722271.
11. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*. 2009;373(9672):1352-1363. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19361855.
12. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS*. 2008;22(7):841-848. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18427202.
13. Palella FJ, Jr., Deloria-Knoll M, Chmiel JS, et al. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. *Ann Intern Med*. 2003;138(8):620-626. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12693883.
14. Cain LE, Logan R, Robins JM, et al. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study. *Ann Intern Med*. 2011;154(8):509-515. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21502648.
15. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. 2010;363(3):257-265. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20647201.
16. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009;360(18):1815-1826. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19339714.
17. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1 seroconverters. *Arch Intern Med*. 2011;171(17):1560-1569. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21949165.
18. Emery S, Neuhaus JA, Phillips AN, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis*. 2008;197(8):1133-1144. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18476292.
19. Grinsztejn B HM, Swindells S, et al. Effect of early versus delayed initiation of antiretroviral therapy (ART) on clinical outcomes in the HPTN 052 randomized clinical trial. Paper presented at: AIDS 2012 Conference. 2012, Washington, DC. Abs ThLBB05.
20. Hogan CM, Degruittola V, Sun X, et al. The setpoint study (ACTG A5217): effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1-infected individuals. *J Infect Dis*. 2012;205(1):87-96. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22180621>.
21. Geng EH, Hare CB, Kahn JO, et al. The effect of a "universal antiretroviral therapy" recommendation on HIV RNA levels among HIV-infected patients entering care with a CD4 count greater than 500/μL in a public health setting. *Clin Infect Dis*. 2012;55(12):1690-1697. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22955429>.
22. Mellors JW, Rinaldo CR, Jr., Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science*. 1996;272(5265):1167-1170. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8638160.
23. Vlahov D, Graham N, Hoover D, et al. Prognostic indicators for AIDS and infectious disease death in HIV-infected injection drug users: plasma viral load and CD4+ cell count. *JAMA*. 1998;279(1):35-40. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9424041.
24. Anastos K, Kalish LA, Hessel N, et al. The relative value of CD4 cell count and quantitative HIV-1 RNA in predicting

- survival in HIV-1-infected women: results of the women's interagency HIV study. *AIDS*. 1999;13(13):1717-1726. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10509574.
25. O'Brien TR, Blattner WA, Waters D, et al. Serum HIV-1 RNA levels and time to development of AIDS in the Multicenter Hemophilia Cohort Study. *JAMA*. 1996;276(2):105-110. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8656501.
 26. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet*. 2002;360(9327):119-129. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12126821.
 27. Anastos K, Barron Y, Cohen MH, et al. The prognostic importance of changes in CD4+ cell count and HIV-1 RNA level in women after initiating highly active antiretroviral therapy. *Ann Intern Med*. 2004;140(4):256-264. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14970148.
 28. O'Brien WA, Hartigan PM, Martin D, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. Veterans Affairs Cooperative Study Group on AIDS. *N Engl J Med*. 1996;334(7):426-431. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8552144.
 29. Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team. *Ann Intern Med*. 1997;126(12):929-938. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9182469.
 30. Chene G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. *Lancet*. 2003;362(9385):679-686. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12957089.
 31. Deeks SG, Gange SJ, Kitahata MM, et al. Trends in multidrug treatment failure and subsequent mortality among antiretroviral therapy-experienced patients with HIV infection in North America. *Clin Infect Dis*. 2009;49(10):1582-1590. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19845473.
 32. Mugavero MJ, Napravnik S, Cole SR, et al. Viremia copy-years predicts mortality among treatment-naive HIV-infected patients initiating antiretroviral therapy. *Clin Infect Dis*. 2011;53(9):927-935. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21890751.
 33. Reekie J, Gatell JM, Yust I, et al. Fatal and nonfatal AIDS and non-AIDS events in HIV-1-positive individuals with high CD4 cell counts according to viral load strata. *AIDS*. 2011;25(18):2259-2268. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21918422.
 34. Szczech LA, Gupta SK, Habash R, et al. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int*. 2004;66(3):1145-1152. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15327410.
 35. Marras D, Bruggeman LA, Gao F, et al. Replication and compartmentalization of HIV-1 in kidney epithelium of patients with HIV-associated nephropathy. *Nat Med*. 2002;8(5):522-526. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11984599.
 36. Estrella M, Fine DM, Gallant JE, et al. HIV type 1 RNA level as a clinical indicator of renal pathology in HIV-infected patients. *Clin Infect Dis*. 2006;43(3):377-380. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16804855.
 37. Atta MG, Gallant JE, Rahman MH, et al. Antiretroviral therapy in the treatment of HIV-associated nephropathy. *Nephrol Dial Transplant*. 2006;21(10):2809-2813. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16864598.
 38. Schwartz EJ, Szczech LA, Ross MJ, Klotman ME, Winston JA, Klotman PE. Highly active antiretroviral therapy and the epidemic of HIV+ end-stage renal disease. *J Am Soc Nephrol*. 2005;16(8):2412-2420. Available at

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15987747.

39. Kalayjian RC, Franceschini N, Gupta SK, et al. Suppression of HIV-1 replication by antiretroviral therapy improves renal function in persons with low CD4 cell counts and chronic kidney disease. *AIDS*. 2008;22(4):481-487. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18301060.
40. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS*. 2008;22(15):1979-1991. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18784461.
41. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002;360(9349):1921-1926. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12493258.
42. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med*. 2012;156(4):271-278. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22351712>.
43. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. Aug 14-28 2006;166(15):1632-1641. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16908797.
44. Balagopal A, Philp FH, Astemborski J, et al. Human immunodeficiency virus-related microbial translocation and progression of hepatitis C. *Gastroenterology*. 2008;135(1):226-233. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18457674.
45. Blackard JT, Kang M, St Clair JB, et al. Viral factors associated with cytokine expression during HCV/HIV co-infection. *J Interferon Cytokine Res*. 2007;27(4):263-269. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17477814.
46. Hong F, Tuyama A, Lee TF, et al. Hepatic stellate cells express functional CXCR4: role in stromal cell-derived factor-1alpha-mediated stellate cell activation. *Hepatology*. 2009;49(6):2055-2067. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19434726.
47. Macias J, Berenguer J, Japon MA, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfecting with human immunodeficiency virus/hepatitis C virus. *Hepatology*. 2009;50(4):1056-1063. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19670415.
48. Verma S, Goldin RD, Main J. Hepatic steatosis in patients with HIV-Hepatitis C Virus coinfection: is it associated with antiretroviral therapy and more advanced hepatic fibrosis? *BMC Res Notes*. 2008;1:46. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18710499.
49. Ragni MV, Nalesnik MA, Schillo R, Dang Q. Highly active antiretroviral therapy improves ESLD-free survival in HIV-HCV co-infection. *Haemophilia*. 2009;15(2):552-558. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19347994.
50. Matthews GV, Avihingsanon A, Lewin SR, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV coinfecting antiretroviral naive individuals in Thailand. *Hepatology*. 2008;48(4):1062-1069. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18697216.
51. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology*. 2006;44(5):1110-1116. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17058225.
52. Avidan NU, Goldstein D, Rozenberg L, et al. Hepatitis C viral kinetics during treatment with peg IFN-alpha-2b in HIV/HCV coinfecting patients as a function of baseline CD4+ T-cell counts. *J Acquir Immune Defic Syndr*. 2009;52(4):452-458. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19797971.

53. Limketkai BN, Mehta SH, Sutcliffe CG, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfecting with HIV/HCV. *JAMA*. 2012;308(4):370-378. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22820790>.
54. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet*. 2007;369(9568):1169-1178. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17416261.
55. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med*. 2008;359(4):339-354. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18650512.
56. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr*. 2010;53(3):323-332. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20032785.
57. Loko MA, Bani-Sadr F, Valantin MA, et al. Antiretroviral therapy and sustained virological response to HCV therapy are associated with slower liver fibrosis progression in HIV-HCV-coinfecting patients: study from the ANRS CO 13 HEPAVIH cohort. *Antivir Ther*. 2012;17(7):1335-1343. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23052829>.
58. Brau N, Salvatore M, Rios-Bedoya CF, et al. Slower fibrosis progression in HIV/HCV-coinfecting patients with successful HIV suppression using antiretroviral therapy. *J Hepatol*. 2006;44(1):47-55. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16182404.
59. Thorpe J, Saeed S, Moodie EE, Klein MB, Canadian Co-infection Cohort S. Antiretroviral treatment interruption leads to progression of liver fibrosis in HIV-hepatitis C virus co-infection. *AIDS*. 2011;25(7):967-975. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21330904>.
60. Smith C. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. *AIDS*. 2010;24(10):1537-1548. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20453631.
61. Mocroft A, Reiss P, Gasiorowski J, et al. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. *J Acquir Immune Defic Syndr*. 2010;55(2):262-270. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20700060.
62. Weber R SC, D:A:D Study Group. Trends over time in underlying causes of death in the D:A:D study from 1999 to 2011. Program and abstracts presented at: the XIX International AIDS Conference; 2012; Washington, DC. Abstract THAB0304.
63. Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. *HIV Med*. 2012;13(8):453-468. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22413967>.
64. Althoff KA GS. A critical epidemiologic review of cardiovascular disease risk in HIV-infected adults: The importance of the HIV-uninfected comparison group, confounding, and competing risks. *HIV Medicine*. 2013;14(3):191-192. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23368691>.
65. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356(17):1723-1735. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17460226.
66. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. 2008;371(9622):1417-1426. Available at

- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18387667.
67. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17135583.
 68. McComsey G, Smith K, Patel P, et al. Similar reductions in markers of inflammation and endothelial activation after initiation of abacavir/lamivudine or tenofovir/emtricitabine: The HEAT Study. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections. 2009. Montreal, Canada.
 69. Torriani FJ, Komarow L, Parker RA, et al. Endothelial function in human immunodeficiency virus-infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy: The ACTG (AIDS Clinical Trials Group) Study 5152s. *J Am Coll Cardiol*. 2008;52(7):569-576. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18687253.
 70. Phillips AN, Neaton J, Lundgren JD. The role of HIV in serious diseases other than AIDS. *AIDS*. 2008;22(18):2409-2418. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19005264.
 71. Baker JV, Duprez D, Rapkin J, et al. Untreated HIV infection and large and small artery elasticity. *J Acquir Immune Defic Syndr*. 2009;52(1):25-31. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19731451.
 72. Marin B, Thiebaut R, Bucher HC, et al. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. *AIDS*. 2009;23(13):1743-1753. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19571723.
 73. Bedimo RJ, McGinnis KA, Dunlap M, Rodriguez-Barradas MC, Justice AC. Incidence of non-AIDS-defining malignancies in HIV-infected versus noninfected patients in the HAART era: impact of immunosuppression. *J Acquir Immune Defic Syndr*. 2009. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19617846.
 74. Silverberg MJ, Chao C, Leyden WA, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. *Cancer Epidemiol Biomarkers Prev*. 2011;20(12):2551-2559. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22109347>.
 75. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst*. 2011;103(9):753-762. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21483021.
 76. Guiguet M, Boue F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol*. 2009. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19818686.
 77. Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS*. 2008;22(16):2143-2153. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18832878.
 78. Reekie J, Kosa C, Engsig F, et al. Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies. *Cancer*. 2010;116(22):5306-5315. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20661911.
 79. Bruyand M, Thiebaut R, Lawson-Ayayi S, et al. Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. *Clin Infect Dis*. 2009;49(7):1109-1116. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19705973.
 80. Silverberg MJ, Chao C, Leyden WA, et al. HIV infection and the risk of cancers with and without a known infectious cause. *AIDS*. 2009;23(17):2337-2345. Available at

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19741479.

81. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*. 2007;370(9581):59-67. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17617273.
82. Zoufaly A, Stellbrink HJ, Heiden MA, et al. Cumulative HIV viremia during highly active antiretroviral therapy is a strong predictor of AIDS-related lymphoma. *J Infect Dis*. 2009;200(1):79-87. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19476437.
83. Shiels MS, Pfeiffer RM, Hall HI, et al. Proportions of Kaposi sarcoma, selected non-Hodgkin lymphomas, and cervical cancer in the United States occurring in persons with AIDS, 1980-2007. *JAMA*. 2011;305(14):1450-1459. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21486978.
84. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. *Ann Intern Med*. 2008;148(10):728-736. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18490686.
85. Simard EP, Pfeiffer RM, Engels EA. Cumulative incidence of cancer among individuals with acquired immunodeficiency syndrome in the United States. *Cancer*. 2011;117(5):1089-1096. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20960504.
86. Silverberg MJ, Neuhaus J, Bower M, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. *AIDS*. 2007;21(14):1957-1963. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17721103>.
87. Neuhaus J, Jacobs DR, Jr., Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *J Infect Dis*. 2010;201(12):1788-1795. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20446848.
88. Ellis RJ, Hsia K, Spector SA, et al, for the HIV Neurobehavioral Research Center Group. Cerebrospinal fluid human immunodeficiency virus type 1 RNA levels are elevated in neurocognitively impaired individuals with acquired immunodeficiency syndrome. *Ann Neurol*. 1997;42(5):679-688. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9392566.
89. McArthur JC, McClellon DR, Cronin MF, et al. Relationship between human immunodeficiency virus-associated dementia and viral load in cerebrospinal fluid and brain. *Ann Neurol*. 1997;42(5):689-698. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9392567.
90. Spudich SS, Huang W, Nilsson AC, et al. HIV-1 chemokine coreceptor utilization in paired cerebrospinal fluid and plasma samples: a survey of subjects with viremia. *J Infect Dis*. 2005;191(6):890-898. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15717264.
91. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. *Ann Neurol*. 1986;19(6):517-524. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3729308.
92. Price RW, Brew BJ. The AIDS dementia complex. *J Infect Dis*. 1988;158(5):1079-1083. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3053922.
93. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69(18):1789-1799. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17914061.
94. Snider WD, Simpson DM, Nielsen S, Gold JW, Metroka CE, Posner JB. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann Neurol*. 1983;14(4):403-418. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6314874.
95. d'Arminio Monforte A, Cinque P, Mocroft A, et al. Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Ann Neurol*. 2004;55(3):320-328. Available at

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14991809.

96. Bhaskaran K, Mussini C, Antinori A, et al. Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. *Ann Neurol*. 2008;63(2):213-221. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17894380.
97. Lescure FX, Omland LH, Engsig FN, et al. Incidence and impact on mortality of severe neurocognitive disorders in persons with and without HIV infection: a Danish nationwide cohort study. *Clin Infect Dis*. Jan 15 2011;52(2):235-243. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21288850.
98. Mellgren A, Antinori A, Cinque P, et al. Cerebrospinal fluid HIV-1 infection usually responds well to antiretroviral treatment. *Antivir Ther*. 2005;10(6):701-707. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16218168.
99. Spudich S, Lollo N, Liegler T, Deeks SG, Price RW. Treatment benefit on cerebrospinal fluid HIV-1 levels in the setting of systemic virological suppression and failure. *J Infect Dis*. 2006;194(12):1686-1696. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17109340.
100. Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance Between Cerebral Spinal Fluid and Plasma HIV Replication in Patients with Neurological Symptoms Who Are Receiving Suppressive Antiretroviral Therapy. *Clin Infect Dis*. 2010. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20100092.
101. Eden A, Fuchs D, Hagberg L, et al. HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment. *J Infect Dis*. 2010;202(12):1819-1825. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21050119>.
102. Simioni S, Cavassini M, Annoni JM, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*. 2010;24(9):1243-1250. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19996937.
103. Smurzynski M, Wu K, Letendre S, et al. Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. *AIDS*. 2011;25(3):357-365. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21124201.
104. Munoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Nadir CD4 cell count predicts neurocognitive impairment in HIV-infected patients. *AIDS Res Hum Retroviruses*. 2008;24(10):1301-1307. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18844464>.
105. Heaton RK, Clifford DB, Franklin DR, Jr., et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. 2010;75(23):2087-2096. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21135382.
106. Cornblath DR, McArthur JC. Predominantly sensory neuropathy in patients with AIDS and AIDS-related complex. *Neurology*. 1988;38(5):794-796. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2834669.
107. Ellis RJ, Rosario D, Clifford DB, et al. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER Study. *Arch Neurol*. 2010;67(5):552-558. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20457954.
108. Evans SR, Ellis RJ, Chen H, et al. Peripheral neuropathy in HIV: prevalence and risk factors. *AIDS*. 2011;25(7):919-928. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21330902.
109. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group. Response to combination antiretroviral therapy: variation by age. *AIDS*. 2008;22(12):1463-1473. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18614870.
110. Nogueras M, Navarro G, Anton E, et al. Epidemiological and clinical features, response to HAART, and survival in HIV-

- infected patients diagnosed at the age of 50 or more. *BMC Infect Dis*. 2006;6:159. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17087819.
111. Bosch RJ, Bennett K, Collier AC, Zackin R, Benson CA. Pretreatment factors associated with 3-year (144-week) virologic and immunologic responses to potent antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2007;44(3):268-277. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17146370.
112. Althoff KN, Justice AC, Gange SJ, et al. Virologic and immunologic response to HAART, by age and regimen class. *AIDS*. 2010;24(16):2469-2479. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20829678.
113. Fahey JL, Taylor JM, Detels R, et al. The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type 1. *N Engl J Med*. 1990;322(3):166-172. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1967191.
114. Giorgi JV, Lyles RH, Matud JL, et al. Predictive value of immunologic and virologic markers after long or short duration of HIV-1 infection. *J Acquir Immune Defic Syndr*. 2002;29(4):346-355. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11917238.
115. Deeks SG, Kitchen CM, Liu L, et al. Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load. *Blood*. 2004;104(4):942-947. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15117761.
116. Giorgi JV, Hultin LE, McKeating JA, et al. Shorter survival in advanced human immunodeficiency virus type 1 infection is more closely associated with T lymphocyte activation than with plasma virus burden or virus chemokine coreceptor usage. *J Infect Dis*. 1999;179(4):859-870. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10068581.
117. Hazenberg MD, Otto SA, van Benthem BH, et al. Persistent immune activation in HIV-1 infection is associated with progression to AIDS. *AIDS*. 2003;17(13):1881-1888. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12960820.
118. Gandhi RT, Spritzler J, Chan E, et al. Effect of baseline- and treatment-related factors on immunologic recovery after initiation of antiretroviral therapy in HIV-1-positive subjects: results from ACTG 384. *J Acquir Immune Defic Syndr*. 2006;42(4):426-434. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16810109.
119. Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. *J Infect Dis*. 2003;187(10):1534-1543. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12721933.
120. Valdez H, Connick E, Smith KY, et al. Limited immune restoration after 3 years' suppression of HIV-1 replication in patients with moderately advanced disease. *AIDS*. 2002;16(14):1859-1866. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12351945.
121. Robbins GK, Spritzler JG, Chan ES, et al. Incomplete reconstitution of T cell subsets on combination antiretroviral therapy in the AIDS Clinical Trials Group protocol 384. *Clin Infect Dis*. 2009;48(3):350-361. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19123865.
122. Lange CG, Lederman MM, Medvik K, et al. Nadir CD4+ T-cell count and numbers of CD28+ CD4+ T-cells predict functional responses to immunizations in chronic HIV-1 infection. *AIDS*. 2003;17(14):2015-2023. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14502004.
123. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med*. 2008;5(10):e203. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18942885.

124. Sandler NG, Wand H, Roque A, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis*. 2011;203(6):780-790. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21252259>.
125. Burdo TH, Lentz MR, Autissier P, et al. Soluble CD163 made by monocyte/macrophages is a novel marker of HIV activity in early and chronic infection prior to and after anti-retroviral therapy. *J Infect Dis*. 2011;204(1):154-163. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21628670>.
126. Palella FJ, Jr., Gange SJ, Benning L, et al. Inflammatory biomarkers and abacavir use in the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study. *AIDS*. 2010;24(11):1657-1665. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20588104.
127. Rodger AJ, Fox Z, Lundgren JD, et al. Activation and coagulation biomarkers are independent predictors of the development of opportunistic disease in patients with HIV infection. *J Infect Dis*. 2009;200(6):973-983. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19678756.
128. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. 2010;50(4):585-596. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20070234>.
129. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf>.
130. Vernazza PL, Troiani L, Flepp MJ, et al. Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV. The Swiss HIV Cohort Study. *AIDS*. 2000;14(2):117-121. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10708281.
131. Coombs RW, Reichelderfer PS, Landay AL. Recent observations on HIV type-1 infection in the genital tract of men and women. *AIDS*. 2003;17(4):455-480. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12598766.
132. Tovnanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *J Acquir Immune Defic Syndr*. 2002;29(3):275-283. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11873077.
133. Kayitenkore K, Bekan B, Rufagari J, et al. The impact of ART on HIV transmission among HIV serodiscordant couples. Paper presented at: XVI International AIDS Conference. 2006. Toronto, Canada.
134. Reynolds S, Makumbi F, Kagaayi J, et al. ART reduced the rate of sexual transmission of HIV among HIV-discordant couples in rural Rakai, Uganda. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections. 2009. Montreal, Canada.
135. Sullivan P, Kayitenkore K, Chomba E, et al. Reduction of HIV transmission risk and high risk sex while prescribed ART: Results from discordant couples in Rwanda and Zambia. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections. 2009. Montreal, Canada.
136. Bunnell R, Ekwaru JP, Solberg P, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS*. 2006;20(1):85-92. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16327323.
137. Castilla J, Del Romero J, Hernando V, Marincovich B, Garcia S, Rodriguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *J Acquir Immune Defic Syndr*. 2005;40(1):96-101. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16123689.
138. Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a model-based analysis. *Lancet*. 2008;372(9635):314-320. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18657710.

139. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis*. 2010;201(3):318-330. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20039804.
140. Uy J, Armon C, Buchacz K, Wood K, Brooks JT. Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *J Acquir Immune Defic Syndr*. 2009;51(4):450-453. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19474757.
141. Abraham AG, Lau B, Deeks S, et al. Missing data on the estimation of the prevalence of accumulated human immunodeficiency virus drug resistance in patients treated with antiretroviral drugs in north america. *Am J Epidemiol*. 2011;174(6):727-735. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21813792>.
142. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med*. 2001;344(11):824-831. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11248160.
143. Schackman BR, Goldie SJ, Weinstein MC, Losina E, Zhang H, Freedberg KA. Cost-effectiveness of earlier initiation of antiretroviral therapy for uninsured HIV-infected adults. *Am J Public Health*. 2001;91(9):1456-1463. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11527782.
144. Mauskopf J, Kitahata M, Kauf T, Richter A, Tolson J. HIV antiretroviral treatment: early versus later. *J Acquir Immune Defic Syndr*. 2005;39(5):562-569. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16044008.
145. Chen RY, Accortt NA, Westfall AO, et al. Distribution of health care expenditures for HIV-infected patients. *Clin Infect Dis*. 2006;42(7):1003-1010. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16511767.
146. Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. *J Acquir Immune Defic Syndr*. 2009;51(2):130-134. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19365271.
147. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis*. 2005;41(10):1483-1497. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16231262.
148. Velasco M, Castilla V, Sanz J, et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. *J Acquir Immune Defic Syndr*. 2009;50(2):148-152. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19131895.
149. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010;362(8):697-706. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20181971.
150. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. 2011;365(16):1492-1501. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010915.
151. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365(16):1471-1481. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010913.
152. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365(16):1482-1491. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010914.

153. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58(RR-4):1-207. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19357635.
154. Lu M, Safren SA, Skolnik PR, et al. Optimal recall period and response task for self-reported HIV medication adherence. *AIDS Behav*. 2008;12(1):86-94. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17577653.
155. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav*. 2006;10(3):227-245. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16783535.
156. Bisson GP, Gross R, Bellamy S, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. *PLoS Med*. 2008;5(5):e109. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18494555.
157. Kalichman SC, Amaral CM, Cherry C, et al. Monitoring medication adherence by unannounced pill counts conducted by telephone: reliability and criterion-related validity. *HIV Clin Trials*. 2008;9(5):298-308. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18977718.
158. Moss AR, Hahn JA, Perry S, et al. Adherence to highly active antiretroviral therapy in the homeless population in San Francisco: a prospective study. *Clin Infect Dis*. 2004;39(8):1190-1198. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15486844.
159. Hunt PW, Brenchley J, Sinclair E, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. *J Infect Dis*. 2008;197(1):126-133. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18171295.
160. Choudhary SK, Vrisekoop N, Jansen CA, et al. Low immune activation despite high levels of pathogenic human immunodeficiency virus type 1 results in long-term asymptomatic disease. *J Virol*. 2007;81(16):8838-8842. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17537849.
161. Egger M. Outcomes of ART in resource-limited and industrialized countries. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections. 2007. Los Angeles, CA.
162. Wolbers M, Bucher HC, Furrer H, et al. Delayed diagnosis of HIV infection and late initiation of antiretroviral therapy in the Swiss HIV Cohort Study. *HIV Med*. 2008;9(6):397-405. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18410354.
163. Grigoryan A, Hall HI, Durant T, Wei X. Late HIV diagnosis and determinants of progression to AIDS or death after HIV diagnosis among injection drug users, 33 US States, 1996-2004. *PLoS One*. 2009;4(2):e4445. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19214229.
164. Centers for Disease Control and Prevention (CDC). Late HIV testing - 34 states, 1996-2005. *MMWR Morb Mortal Wkly Rep*. 2009;58(24):661-665. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19553901.
165. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55(RR-14):1-17. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16988643.