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Effect of Persistency of First-Line HIV Antiretroviral Therapy on Clinical Outcomes

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Abstract

Persistency is the time from initiation to discontinuation of therapy. Previous research has described factors that affect the persistency of initial antiretroviral therapy (ART); however, the impact of persistency on clinical outcomes is unknown. A retrospective study was conducted of treatment-naive HIV patients initiating ART between January 1, 2000 and December 31, 2010 at an academic medical center. Descriptive statistics and Cox proportional hazards regression models with persistency as a time-varying covariate were fit for (1) immunologic failure (subsequent CD4 lower than initial CD4); (2) development of an opportunistic infection (OI) or malignancy; and (3) mortality. Analyses were repeated with an interaction term of persistency (per 180 days) and time (before and after 1 year of ART). Among 879 patients who started ART, the mean age was 38 years (±10) and most patients were racial/ethnic minority (59%), males (80%), and with baseline CD4 <200 cells/mm^3 (52%). There were 100 deaths, 94 OIs/malignancy, and 183 immunologic failures; the mean persistency = 723 days. In multivariable modeling, increased persistency decreased the overall and long-term hazard for immunologic failure (0.84 per 180 additional days; 0.70–1.00; 0.045). Increased persistency exhibited a potential trend toward decreased hazard for the occurrence of OI/malignancy (0.91; 0.80–1.03; 0.124) overall and after 1 year. Persistency exhibited a trend toward less risk of mortality in the first year of ART (0.42; 0.17–1.06; 0.067). In this study of the relationship between initial ART persistency and clinical outcomes, increased persistency was associated with a decreased hazard for the development of immunologic failure, a trend toward a decreased hazard for OI/malignancy, and a trend toward a decreased risk of first year mortality. Given these findings, the relationship between persistency and clinical outcomes merits further study.

Introduction

Persistency is defined as the duration of pharmacologic treatment, from initiation to change of therapy. It represents an operationally distinct construct than adherence, which quantifies the extent to which an individual abides by the dose, frequency, and timing of administration for a prescribed therapy.[1] Multiple factors at the patient level (affective mental health disorder, gender, etc.) and the regimen level (pill burden, frequency of administration, efficacy, tolerability, etc.) can affect persistency. In HIV care, initial antiretroviral therapy (ART) combinations are known to exhibit the longest persistency.[2–8]

ART has transformed HIV into a chronic illness with a life expectancy approaching that of the general population, and ongoing initiatives to increase testing in routine treatment settings and current epidemiologic trends point to HIV being diagnosed in younger individuals.[9–14] In this context, ART regimen persistency is increasingly important to HIV care providers now faced with the need to provide effective ART for decades with a finite number of antiretroviral drugs. While finite treatment options and the increased cost and complexity of post-first line regimens underscore the importance of persistency, the present study explores the impact of increased persistency on clinical outcomes, an issue scarcely addressed in the extant literature. Our objective then was to explore the impact of persistency on three clinical outcomes: (1) immunologic failure; (2) development of an opportunistic infection (OI) or malignancy; and (3) mortality. The impact of these outcomes was measured overall, in

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early (<365 days) and late (>365 days) time periods from ART initiation.

Materials and Methods

This retrospective cohort study used data from the University of Alabama at Birmingham (UAB) 1917 HIV/AIDS Clinic Cohort Observational Database Project, a prospective cohort study containing detailed sociodemographic, psychosocial, and clinical information from over 6,000 clinic patients dating back to 1988. Currently, over 1,900 patients receiving primary and subspecialty HIV care at the clinic participate in the Institutional Review Board (IRB)-approved observational, clinical cohort project. Since August 1, 2004, the UAB 1917 HIV/AIDS Clinic uses a locally developed electronic medical record (EMR) that imports all laboratory values from the central UAB laboratory, requires electronic prescription for all medications, and contains detailed provider encounter notes. The EMR and database are quality controlled, with all provider notes reviewed within 72 h of entry to ensure appropriate data capture regarding changes (additions or deletions) in diagnoses, allergies, and medications, including start and stop dates for antiretroviral and all other prescribed medications. The present study was supported through a collaborative research grant from Definicare, Bristol-Myers Squibb, and Gilead. The study was observational in design and did not provide antiretroviral medications, laboratory tests, or remuneration to participants. Representatives from each research partner participated in the study design, data interpretation, and manuscript preparation but did not contribute to data collection or analysis. Academic authors made the final determination of manuscript content.

Study sample and procedures

All ART-naive patients who initiated therapy while in care at the UAB 1917 Clinic between January 1, 2000 and December 31, 2010 were eligible for inclusion in this retrospective cohort study. Patients who were pregnant within 9 months of the start of ART, who were <19 years old at the start of ART, and whose baseline viral load (VL) was <50 were excluded or those without a valid Social Security number as mortality could not be ascertained via the Social Security Death Index in such cases.

Microsoft SQL queries of our laboratory, diagnostic, administrative, and treatment databases were used to extract data for those who initiated ART at our clinic during the study period. Treatment-naive status at entry into care and all ART prescriptions found in the electronic data were verified through comprehensive review of all provider notes (recorded on paper before August 1, 2004 and electronically after this date). Persistency was then determined, defined as the time from initial ART regimen initiation to change (i.e., therapy augmentation switch or complete discontinuation). Regimens were ended when at least one drug in the regimen was stopped and/or a new drug was added for at least 14 days. Drug changes (including treatment interruptions) lasting less than 14 days did not count as discontinuation. Similarly, dosage changes and simplification (switches to a fixed dose combination of the same drugs) did not count as discontinuation. Each patient's last regimen was ended in a competing risks framework at the earlier of the recorded: stop date, the lost-to-follow-up (LTFU) date, the date of death, or the administrative censoring date (May 11, 2011). A patient was considered as LTFU if they had a gap of more than 210 days (180 days + 30 day buffer) between arrived primary care visits. The LTFU date was defined as the date of last arrived primary care visit before the gap of at least 210 days.

Study variables

Independent variables. Patient level characteristics included sociodemographic (age at ART initiation, gender, race, HIV transmission risk factor, and health insurance status), laboratory (baseline CD4 and viral load), and clinical history (diagnoses of schizophrenia, affective mental health disorder, alcohol or substance abuse). Regimen level characteristics included year of ART initiation and anchoring third drug of initial ART regimens [nucleoside reverse transcriptase inhibitors (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), and integrase inhibitors (II)]. Persistency was calculated as time from initial ART regimen initiation to discontinuation. Persistency was analyzed as a time-varying covariate.

Dependent variables. Three clinical outcome variables were modeled for the study period: (1) immunologic failure defined as subsequent CD4 value lower than initial CD4 value; (2) development (incidence) of an OI (per CDC definitions) or malignancy (composite of all neoplasms AIDS related and non-AIDS related); and (3) mortality as confirmed by the Social Security Death Index (SSDI).

For each outcome the survival time was defined as the time from the start of ART until the event of interest occurred. Patients not experiencing the event were censored at the administrative censoring date (May 11, 2011). For the immunologic failure and development of an OI or malignancy outcomes, death and LTFU were considered to be competing risks. A competing risk is a situation in which the occurrence of one type of event removes the individual from risk of all the other event types. Patients experiencing a competing risk were censored as of the point in time the competing risk occurred. For the immunologic failure outcome only patients with both a baseline CD4 count and at least one available follow-up CD4 before a competing risk were included.

Statistical analyses

Descriptive analyses were used to illustrate the distribution of patient (sociodemographic, clinical, laboratory) and regimen level characteristics and to ensure that the assumptions of subsequent statistical testing were met. Three Cox proportional hazards regression models were fit, one for each of the three dependent variables (immunologic failure; development of an opportunistic infection or malignancy, and mortality). Further analyses for each of the clinical outcomes using a persistency (per 180 days) and time interaction term (before and after 1 year of ART) were performed. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute).

Results

Among 879 study participants, the median age at ART initiation was 38 (IQR 30, 45) years, and the majority were nonwhite (59%, $n = 505$) males (80%, $n = 701$). Men who have

sex with men (MSM) constituted the largest HIV transmission risk group (54%, $n=470$). A total of 52% ($n=424$) of study participants initiated ART with a CD4 < 200 cells/mm^3 and 57% ($n=456$) had a VL ≤ 100,000 copies/ml (Table 1).

There were 100 confirmed deaths (per SSDI), 94 incident combined opportunistic infections or malignancies, and a total of 183 cases of immunologic failure in the observation period. The Kaplan–Meier estimate of the mean persistency of initial ART regimens was 723 days (SD ± 1,012).

Persistency, modeled as a time-varying covariate, was the primary independent variable of interest in the three Cox proportional hazards (PH) models completed, one for each of the three studied clinical outcomes (Table 2).

Immunologic failure

Prolonged initial regimen persistency (per 180 days) was associated with a decreased hazard for immunologic failure (HR 0.84; 95% CI 0.70–1.00; 0.0454). The use of a PI-based initial regimen (HR 1.57; 95% CI 1.09–2.26; 0.0147) and a diagnosis of schizophrenia (HR 2.11; 95% CI 1.10–4.05; 0.0243) were found to increase the hazard of immunologic failure. In the model with the persistency/time interaction term, the long-term hazard for immunologic failure decreased with prolonged persistency (persistency per 180 days/ > 365 days of ART 0.85; 0.72–1.00; 0.0437).

Incident OI or malignancy

Increased persistency (per 180 days) exhibited a potential trend toward decreased hazard for the occurrence of OI/malignancy (0.91; 0.80–1.03; 0.1236). More recent ART initiation (2007–2010) was associated with a decreased hazard for this outcome (HR 0.51; 95% CI 0.26–0.98; 0.0433). In the model with the persistency/time interaction term, the long-term hazard for incident OI or malignancy exhibited a trend toward statistical significance with prolonged persistency (persistency per 180 days/ > 365 days of ART 0.90; 0.80–1.02; 0.0953).

Mortality

Prolonged initial regimen persistency (per 180 days) was not significantly associated with mortality (HR 0.95; 95% CI 0.87–1.04; 0.2808). Baseline CD4 < 200 cells/mm^3 (HR 3.68; 95% CI 1.27–10.65; 0.0165), Public Insurance (HR 2.91; 95% CI 1.65–5.14; 0.0002), and a diagnosis of schizophrenia were associated with increased hazard for mortality (HR 2.72; 95% CI 1.05–7.02; 0.0394). Age group 30–39 vs. ≥ 50 years old (HR 0.48; 95% CI 0.25–0.93; 0.0296) and a diagnosis of affective mental health disorder (0.53; 0.33–0.85; 0.0091) were associated with a decreased hazard for mortality. In the model with the persistency/time interaction term, the hazard for mortality in the first year of ART exhibited a trend toward a statistically significant decrease with prolonged persistency (persistency per 180 days/ < 365 days of ART 0.42; 0.17–1.06; 0.0669).

Discussion

There is a natural tension between prolonged life expectancy on ART and achieving lifelong therapy with a finite number of effective drugs.[9,13,14] Maximizing the persistency of each successive ART regimen is crucial in maximizing

Table 1. Descriptive Statistics of Treatment-Naive Individuals ($n=879$) Starting Antiretroviral Therapy 1/1/2000–5/11/2011 at the UAB 1917 HIV/AIDS Clinic Cohort

Characteristic	*Results* (n, %)
Age at ART initiation (years)	
19–29	195 (22.2)
30–39	301 (34.2)
40–49	255 (29.0)
≥ 50	128 (14.6)
Race (16 missing)	
Nonwhite	505 (58.5)
White	358 (41.5)
Gender	
Female	178 (20.3)
Male	701 (79.7)
Insurance	
Private	333 (37.9)
Public	234 (26.6)
Uninsured	312 (35.5)
HIV risk factor (7 missing)	
Heterosexual	337 (38.7)
IVDU	65 (7.5)
MSM	470 (53.9)
Substance abuse	
No	708 (80.6)
Yes	171 (19.5)
Alcohol abuse	
No	742 (84.4)
Yes	137 (15.6)
Schizophrenia	
No	850 (96.7)
Yes	29 (3.3)
Affective mental health disorder	
No	428 (48.7)
Yes	451 (51.3)
Baseline CD4 (cells/mm^3) (68 missing)	
< 200	424 (52.3)
201–350	238 (29.4)
> 351	149 (18.4)
Baseline $\log_{10}$ VL median (IQR) (84 missing)	4.9 (4.4, 5.5)
ART start	
2000–2003	240 (27.3)
2004–2006	223 (25.4)
2007–2010	416 (47.3)
Third drug[a]	
II	33 (3.8)
NNRTI	628 (71.4)
NRTI	50 (5.7)
PI[b]	168 (19.1)

[a]Of the initial ART regimens 94% ($n=829$) included exactly two NRTIs. In total, 99% ($n=870$) of regimens included either emtricitabine (59%, $n=520$) or lamivudine (40%, $n=350$).

[b]Combined boosted ($n=133$) and unboosted ($n=35$) protease inhibitors.

Reasons for ending persistency: lost to follow-up ($n=366$); adverse event ($n=136$); noncompliant ($n=79$); unknown ($n=47$); therapy failure ($n=38$); death ($n=22$); concomitant medical condition ($n=13$); structured treatment interruption ($n=6$).

ART, antiretroviral therapy; IVDu, intravenous drug use; MSM, men who have sex with men; VL, viral load; II, integrase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2. Multivariable Survival Analyses of the Association of Time-Varying Persistency and Clinical Events (Immunologic Failure, Oportunistic Infection/Malignancy, Death) Among Treatment-Naive Individuals Starting Antiretroviral Therapy 1/1/2000–5/11/2011 at the UAB 1917 HIV/AIDS Clinic Cohort

Characteristic	*Immunologic failure HR (95% CI)*	*OI/malignancy HR (95% CI)*	*Death HR (95% CI)*
Persistency (per 180 days)[a,b]	**0.84 (0.70–1.00)**	0.91 (0.80–1.03)	0.95 (0.87–1.04)
Age at ART initiation (years)			
19–29	0.96 (0.59–1.55)	0.56 (0.24–1.29)	0.61 (0.30–1.27)
30–39	0.71 (0.44–1.12)	0.58 (0.29–1.14)	**0.48 (0.25–0.93)**
40–49	0.70 (0.44–1.11)	0.79 (0.41–1.51)	0.69 (0.37–1.28)
≥50	1.0	1.0	1.0
Race			
White	1.0	1.0	1.0
Nonwhite	0.89 (0.64–1.24)	1.03 (0.60–1.76)	1.60 (0.93–2.76)
Gender			
Male	1.0	1.0	1.0
Female	1.24 (0.84–1.84)	0.77 (0.41–1.46)	0.60 (0.33–1.09)
Insurance			
Private	1.0	1.0	1.0
Public	1.06 (0.71–1.60)	1.07 (0.61–1.88)	**2.91 (1.65–5.14)**
Uninsured	1.01 (0.70–1.46)	0.84 (0.45–1.59)	1.25 (0.65–2.41)
Schizophrenia			
No	1.0	1.0	1.0
Yes	**2.11 (1.10–4.05)**	1.48 (0.42–5.17)	**2.72 (1.05–7.02)**
Affective mental health disorder			
No	1.0	1.0	1.0
Yes	1.30 (0.95–1.79)	1.08 (0.66–1.77)	**0.53 (0.33–0.85)**
Baseline CD4 (cells/mm^3)			
<200	—	2.14 (0.96–4.77)	**3.68 (1.27–10.65)**
200–350		0.84 (0.34–2.11)	2.42 (0.80–7.31)
>350		1.0	1.0
Baseline $\log_{10}$ VL median (IQR)	**0.62 (0.52–0.75)**	1.19 (0.84–1.71)	0.98 (0.71–1.35)
ART start			
2000–2003	1.0	1.0	1.0
2004–2006	1.39 (0.85–2.27)	0.67 (0.37–1.22)	1.34 (0.73–2.46)
2007–2010	1.43 (0.89–2.30)	**0.51 (0.26–0.98)**	0.82 (0.38–1.77)
Third drug			
NNRTI	1.0	1.0	1.0
II	0.99 (0.42–2.33)	1.70 (0.39–7.49)	4.17 (0.91–19.24)
NRTI	1.66 (0.87–3.19)	1.24 (0.49–3.12)	1.90 (0.89–4.07)
PI	**1.57 (1.09–2.26)**	1.24 (0.68–2.28)	0.58–2.02)

[a] p-values for persistency: immunologic failure 0.0454; OI/malignancy 0.1236; death 0.2808.

[b] Persistency/time interaction term results. [Results in bold are significant (p-value<0.05) while results marked with asterisks are marginally significant (0.05<p-value<0.10).] Immunologic failure: Persistency (per 180 days) early (<365 days): 0.66; 0.31–1.39. Persistency (per 180 days) late (>365 days): **0.85; 0.72–1.00.** Incident malignancy/OI: Persistency (per 180 days) early (<365 days): 1.04; 0.25–4.28. Persistency (per 180 days) early (>365 days): 0.90; 0.80–1.02*. Death: Persistency (per 180 days) early (<365 days): 0.42; 0.17–1.06*. Persistency (per 180 days) early (>365 days): 0.97; 0.89–1.05.

OI, oportunistic infection; HR, hazard ratio; CI, confidence interval.

patient life expectancy. While previous studies have identified patient and regimen level factors associated with increased persistency, little is known regarding its impact on and association with clinical outcomes.[2–8] In the present study, we explored the relationship of first ART regimen persistency with three clinical outcomes overall, and before and after the first year of ART initiation. We found evidence of a clear association between prolonged first regimen persistency and decreased hazards for immunologic failure. In addition, although not statistically significant, we saw a trend toward decreased hazards for both the clinical outcome of incident OI or malignancy after 1 year of ART as well as a trend toward decreased mortality in the first year of ART with prolonged first regimen persistency (per 180 days of continuous ART).

Immunologic failure was selected as an outcome due to the well-known risks associated with decreased CD4 values. In this study, immunologic failure was defined as a subsequent value lower than baseline CD4 value during the time after first ART regimen initiation. Prolonged persistency was protective for immunologic failure in primary analysis and after long-term ART initiation in the model with the persistency/time interaction term. Though multiple efficacious treatment options are available, first regimens achieve the greatest persistency. As ART start commonly coincides with CD4 nadirs, the time of ART initiation is a vulnerable period in which the clinical risks for immunologic failure are decreased by prolonged persistency.[8] Framing this finding in the context of providing lifelong ART and decreasing the total number of days a patient is at equal or greater risk of complications associated with a lower

than baseline CD4 while on initial ART underscore the relevance of prolonging persistency to this clinical outcome. Selecting a regimen associated with prolonged persistency at the time of ART initiation will decrease the risks associated with immunologic failure over the long term.

In our second model, a composite clinical outcome of incident OI or malignancy is featured as the dependent variable. Though persistency did not show a statistically significant decreased hazard for this outcome, a trend for increased persistency being protective was found (HR 0.91; 95% CI 0.80–1.03) in the overall model. The model including the persistency/time interaction term showed a similar trend after 1 year of ART therapy. We posit that with a greater sample size, these associations could achieve statistical significance. We also recognize that this is a composite outcome and multiple other questions regarding the association of persistency with specific OIs or malignancies remain unexplored. Defining such associations could influence future regimen selection. For example, we might select regimens with optimized persistency that are known to reduce risk in a person known to have preexisting tendencies to develop a specific malignancy. Defining the relationship between persistency, specific clinical outcomes, and their risk over time with larger datasets will both solidify knowledge about further clinical ramifications of prolonged persistency and potentially inform our treatment decisions in the context of an individual's other preexisting health risks and the need for lifelong ART in the future.

No statistically significant association was found between first ART regimen persistency and subsequent mortality as reported in the SSDI in initial analyses. However, when a persistency/time interaction term was added to the model, we observed a trend toward a decrease in mortality in the first year of ART. This finding may be due to the higher risk of mortality seen in those starting ART with lower baseline CD4 values, a population in which prolonged persistency in the first year will be critical. The question of how much the persistency of initial ART regimen influences the risk of subsequent mortality must be posed, and per these data, the effect seems minimal as multiple factors beyond the persistency of the first regimen are likely to influence long-term mortality risk. Beyond individual mortality risks, however, future studies must gauge the effect of persistency at the community level in terms of HIV transmission. Recent studies point to virologic control as a key strategy to prevent transmission, a notion captured in the "treatment as prevention" paradigm.[15,16] To maximize the impact of such public health strategies, efficacious regimens with prolonged persistency will be needed. The relationship between regimen persistency and its impact on transmission currently remains undefined. In addition, persistency of initial ART is particularly important in resource-limited settings in which limited subsequent therapeutic options and limited monitoring resources make the selection of regimens with optimized persistency crucial to the long-term success of national treatment programs.

The present study must be considered in light of its limitations. First, due to the retrospective observational cohort study design, we are able to determine associations and cannot define causation. Though extensive and meticulous confirmation of all electronic prescriptions was performed by review of all provider notes, patient level data on regimen adherence were not available for analyses. In addition, as a single site cohort drawing patients from a limited geographic region in the United States, the applicability of our findings to other treatment populations and settings must be cautiously considered.

Maximizing persistency becomes increasingly important as epidemiologic trends point to prolonged longevity and trends toward younger transmission and diagnosis in HIV and providers think in terms of providing lifelong successful ART therapy. In this initial study of the impact of prolonged first regimen persistency on clinical outcomes, we found decreased hazards of immunologic failure and a trend toward decreased hazards for incident OI or malignancy in patients on long-term first line therapy as well as a trend toward a decreased hazard of mortality in the first year of ART. Though these initial data begin to underscore the importance of persistency on such outcomes, much work remains on understanding the effect of persistency on clinical outcomes. With such insights, persistency may become a factor to aid in regimen selection in the future.

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References

1. Cramer JA, Roy A, Burrell A, *et al.:* Medication compliance and persistence: Terminology and definitions. Value Health 2008;11(1):44–47.
2. Ahdieh-Grant L, Tarwater PM, Schneider MF, *et al.:* Factors and temporal trends associated with highly active antiretroviral therapy discontinuation in the Women's Interagency HIV Study. J Acquir Immune Defic Syndr 2005;38(4): 500–503.
3. Juday T, Grimm K, Zoe-Powers A, Willig J, and Kim E: A retrospective study of HIV antiretroviral treatment persistence

in a commercially insured population in the United States. AIDS Care 2011;23(9):1154–1162.
4. Vo TT, Ledergerber B, Keiser O, *et al.:* Durability and outcome of initial antiretroviral treatments received during 2000–2005 by patients in the Swiss HIV Cohort Study. J Infect Dis 2008;197(12):1685–1694.
5. Willig JH, Abroms S, Westfall AO, *et al.:* Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy. AIDS 2008;22(15):1951–1960.
6. Willig JH, Echevarria J, Westfall AO, *et al.:* Durability of initial antiretroviral therapy in a resource-constrained setting and the potential need for zidovudine weight-based dosing. J Acquir Immune Defic Syndr 2010;53(2):215–221.
7. Kempf MC, Pisu M, Dumcheva A, Westfall AO, Kilby JM, and Saag MS: Gender differences in discontinuation of antiretroviral treatment regimens. J Acquir Immune Defic Syndr 2009;52(3):336–341.
8. Chen RY, Westfall AO, Mugavero MJ, *et al.:* Duration of highly active antiretroviral therapy regimens. Clin Infect Dis 2003;37(5):714–722.
9. The Antiretroviral Cohort Collaboration: Life expectancy of individuals on combination antiretroviral therapy in high-income countries: A collaborative analysis of 14 cohort studies. Lancet 2008;372(9635):293–299.
10. Lieb S, Prejean J, Thompson DR, *et al.:* HIV prevalence rates among men who have sex with men in the southern United States: Population-based estimates by race/ethnicity. AIDS Behav 2011;15(3):596–606.
11. May M, Gompels M, Delpech V, *et al.:* Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. BMJ 2011;343:d6016.
12. Mills EJ, Bakanda C, Birungi J, *et al.:* Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: A cohort analysis from Uganda. Ann Intern Med 2011;155(4):209–216.
13. Nakagawa F, Lodwick RK, Smith CJ, *et al.:* Projected life expectancy of people with HIV according to timing of diagnosis. AIDS 2012;26(3):335–343.
14. Prejean J, Song R, Hernandez A, *et al.:* Estimated HIV incidence in the United States, 2006–2009. PLoS One 2011; 6(8):e17502.
15. 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.
16. Das M, Chu PL, Santos GM, *et al.:* Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. PLoS One 2010;5(6):e11068.

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