

Retention in Care: A Challenge to Survival with HIV Infection

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(See the editorial commentary by Cheever on pages 1500–2)

Background. Patients with human immunodeficiency virus (HIV) infection need lifelong medical care, but many do not remain in care. The effect of poor retention in care on survival is not known, and we sought to quantify that relationship.

Methods. We conducted a retrospective cohort study involving persons newly identified as having HIV infection during 1997–1998 at any United States Department of Veterans Affairs hospital or clinic who started antiretroviral therapy after 1 January 1997. To be included in the study, patients had to have seen a clinician at least once after receiving their first antiretroviral prescription and to have survived for at least 1 year. Patients were divided into 4 groups on the basis of the number of quarters in that year during which they had at least 1 HIV primary care visit. Survival was measured through 2002. Because data were available for only a small number of women, female patients were excluded from the study.

Results. A total of 2619 men were followed up for a mean of >4 years each. The median baseline CD4⁺ cell count and median log₁₀ plasma HIV concentration were 228 × 10⁶ cells/L and 4.58 copies/mL, respectively. Thirty-six percent of the patients had visits in <4 quarters, and 16% died during follow-up. In Cox multivariate regression analysis, compared with persons with visits in all 4 quarters during the first year, the adjusted hazard ratio of death was 1.42 (95% confidence interval, 1.11–1.83; *P* < .01), 1.67 (95% confidence interval, 1.24–2.25; *P* < .001), and 1.95 (95% confidence interval, 1.37–2.78; *P* < .001) for persons with visits in 3 quarters, 2 quarters, and 1 quarter, respectively.

Conclusions. Even in a system with few financial barriers to care, a substantial portion of HIV-infected patients have poor retention in care. Poor retention in care predicts poorer survival with HIV infection. Retaining persons in care may improve survival, and optimal methods to retain patients need to be defined.

HAART has resulted in dramatic improvements in survival for persons with HIV infection, with the result that HIV infection is considered to be a manageable, chronic disease [1, 2]. To maximally benefit from HAART, persons with HIV infection must receive a diagnosis before an advanced stage of immunosup-

pression and then enter quality HIV care [3]. Once they access care, HIV-infected patients must remain in care indefinitely. The success that patients with HIV infection have in remaining in care has only been described in limited studies [4–7], yet national data suggest that as many as one-half of the patients who know that they have HIV infection in the United States are not in routine care [8]. Although it may seem intuitive that persons who remain in medical care will live longer than persons who do not, that relationship has not been demonstrated for HIV infection or, for that matter, for other chronic diseases.

Persons with HIV infection may be an ideal population in which to study the relationship between retention in care and survival. Without treatment, HIV infection is usually fatal within a decade, but with suc-

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successful long-term treatment of HIV infection, life expectancy is extended by many years or even decades [9–12]. Widely accepted treatment guidelines from the US Department of Health and Human Services have long recommended that HIV-infected patients receiving antiretroviral therapy be seen every 3–4 months [13]. Finally, persons living with HIV infection are often socially vulnerable and experience stigma and, therefore, may have difficulty remaining in care [4, 5, 14]. Although the relationship between retention in care and survival may be partially mediated by adherence to HAART, patients who are out of care cannot receive treatment for medical and psychiatric comorbid conditions or the careful monitoring that is required when taking HAART, let alone receive interventions to improve adherence to therapy. Poor retention in care is a potentially correctable cause of suboptimal health outcomes and may be associated with racial and socioeconomic disparities in outcomes.

The Department of Veterans Affairs (VA), which has endorsed the Department of Health and Human Services treatment guidelines, is the largest provider of HIV care in the United States. It maintains system-wide clinical, service use, and death data in a national registry of HIV-infected patients [15]. We used the VA registry to study retention in care after starting antiretroviral therapy, hypothesizing that poor retention in care would be associated with adverse clinical outcomes, including death.

METHODS

Data source. The VA Immunology Case Registry was established nationwide in 1992, and it has been described elsewhere [15, 16]. It draws upon the electronic medical records of the nearly 60,000 HIV-infected patients cared for by the VA since the registry's inception. Veterans with HIV infection are registered at local VA facilities, after which all past clinical data are electronically retrieved. The database is automatically electronically updated from local sites on a daily basis. Periodic surveys and chart reviews have been undertaken to verify that the registry's population is accurate and complete. The registry includes all demographic, laboratory, pharmacy, outpatient clinic visit, and hospitalization data, as well as dates of death. For the present study, VA data on deaths were supplemented with data from the National Death Index.

Subjects. The study population comprised HIV-positive veterans who were entered into the registry between 1 January 1997 and 31 December 1998 and who initiated outpatient primary care, including antiretroviral therapy, with the VA. Patients were included if: (1) their first VA prescription for an antiretroviral medication was on or after 1 January 1997; (2) they had an "index visit" for HIV primary care, defined as an outpatient visit at an infectious disease, internal medicine, primary care, or immunology clinic on or after the date of their

first VA antiretroviral prescription; (3) they had a baseline CD4⁺ cell count available; and (4) they survived ≥ 1 year after the index visit. These criteria minimized inclusion of patients relying on the VA solely for pharmacy benefits, allowed for disease-severity adjustment, and assured an adequate observation time in which to assess retention in care.

Definitions of variables. Retention in care during the first year of antiretroviral treatment was operationalized by dividing the year after the index visit into 3-month quarters and examining the dates of all HIV primary care provider visits during that year. Each patient was then categorized as having had at least 1 HIV primary care provider visit in 4, 3, 2, or 1 of those quarters.

The baseline CD4⁺ cell count and plasma HIV concentration were values obtained ≤ 180 days before the first antiretroviral prescription date, preferentially using the value obtained closest to that date. A plasma HIV concentration < 500 copies/mL was considered to be "undetectable" and was assigned a value of 200 copies/mL for computational purposes. Plasma HIV concentrations greater than the upper limit of quantification were assigned the value of the upper limit of quantification.

To quantify non-HIV-related comorbidities, we applied Deyo's modification of the Charlson score (minus the diagnosis of HIV infection) to diagnoses recorded in the year before the index visit [17]. Hepatitis C virus infection was defined as present in patients with an antibody test result positive for hepatitis C virus at or before the index visit. HAART use was defined as the use of a protease inhibitor, nonnucleoside reverse-transcriptase inhibitor, or combination of zidovudine, lamivudine, and abacavir within 30 days of the first antiretroviral prescription. Alcohol abuse, hard illicit drug use, and socioeconomic instability were defined by *International Classification of Diseases, Ninth Revision*, codes (available upon request) from any inpatient or outpatient encounter up to and including the index visit.

Outcomes. The main outcome was survival. Because survival for 1 year was an inclusion criterion, follow-up for the survival analyses began 365 days after the index visit and ended at death or 31 December 2002, whichever came first. Secondary outcomes were changes from baseline in CD4⁺ cell count and plasma HIV concentration 1 year (± 90 days) after initiating antiretroviral therapy.

Statistical analysis. Continuous data were compared with analysis of variance for normally distributed data and with the Kruskal-Wallis test for nonnormally distributed data. Categorical data were compared with the χ^2 test. Kaplan-Meier plots were constructed and compared with the log-rank test. To adjust for potential confounders and baseline disease severity, Cox proportional hazards modeling was performed. Statistics were analyzed with SAS software (SAS Institute). The study was approved by the Institutional Review Board for Baylor College of

Medicine and Affiliated Institutions, as well as by the VA. Individual informed consent was not required.

RESULTS

Cohort and baseline characteristics. The registry included 4752 patients entered into the database in 1997 and 1998 with HIV and outpatient visit data. Of these patients, 3691 (78%) were first prescribed an antiretroviral medication on or after 1 January 1997 and had a VA primary care visit on or after the date of their first antiretroviral prescription. There were 255 patients who died within 1 year after the index primary care visit, leaving 3436 patients. Baseline CD4⁺ cell count results were available for 2673 (78%) of these remaining patients. Of the 2673 patients, 54 were women; these women were dropped from further analysis because of the small sample size. The remaining cohort of 2619 men included 55% of the original sample. The 2133 patients not included in the study were also nearly all men (male sex, 95%), but compared with the study cohort, they were a mean of almost 1 year older and were more likely to have missing data for race/ethnicity. The final analysis cohort of 2619 men represents HIV-infected male veterans who used the VA health care system and who started antiretroviral therapy during the defined study interval with a baseline CD4⁺ cell count result available who survived for at least 1 year.

The baseline characteristics of the analysis cohort are presented in table 1. Of note, HIV disease was advanced in most patients, with a median initial CD4⁺ cell count of 228×10^6 cells/L. More than 80% of patients were given a first antiretroviral regimen that qualified as HAART; the remaining patients were given other antiretroviral regimens. The subjects were divided into 4 groups on the basis of the number of quarters of the first year after starting antiretroviral therapy during which they had at least 1 outpatient HIV provider visit; 64% of the subjects had visits in 4 of 4 quarters, 18% had visits in 3 of 4 quarters, 11% had visits in 2 of 4 quarters, and 6% had visits in 1 of 4 quarters.

Baseline differences were found between the 4 groups with respect to known predictors of HIV disease survival, including age, race/ethnicity, CD4⁺ cell count, plasma HIV concentration, HAART use, and hepatitis C virus coinfection (table 1). In general, the persons with better retention in care had more-advanced disease, were older, and had received HAART slightly more often. They also had less hepatitis C virus coinfection, less alcohol use, and less hard illicit drug use. There were no differences in the prevalence of non-HIV-related comorbidities or socioeconomic instability.

Outcomes. CD4⁺ cell count and plasma HIV concentration data after 1 year of antiretroviral therapy were less often available for patients with worse retention in care. However, even for patients with available data, poor retention in care was

associated with less improvement in CD4⁺ cell count and less reduction in plasma HIV level at 1 year (table 2).

Deaths after 1 year occurred in 425 patients (16% of the sample population). The unadjusted death rates trended higher with worse retention in care ($P = .06$). Kaplan-Meier results for >4 years of follow-up show that the group with visits in 1 of 4 quarters had the worst survival, whereas the group with visits in 4 of 4 quarters had the best survival ($P = .02$; figure 1).

Multivariate analysis adjusted for potential confounders to the relationship between retention in care and survival (table 3). The model included the entire analysis cohort and adjusted for age, race/ethnicity, baseline CD4⁺ cell count, receipt of HAART, hepatitis C virus coinfection, non-HIV-related comorbidity score, alcohol abuse, hard illicit drug use, and socioeconomic instability. After adjustment, poor retention in care was associated with poorer survival, with a dose-response relationship. Compared with persons who had visits in all 4 quarters, the adjusted hazard ratio of death was 1.42 (95% CI, 1.11–1.83; $P < .01$), 1.67 (95% CI, 1.24–2.25; $P < .001$), and 1.95 (95% CI, 1.37–2.78; $P < .001$) for persons with visits in 3, 2, and 1 quarter, respectively. Lower baseline CD4⁺ cell count, older age, a greater number of non-HIV-related comorbidities, and hepatitis C virus coinfection were also associated with increased risk of death.

Confirmatory analyses. We conducted a number of additional analyses to confirm these results. We added baseline plasma HIV concentration to the model (2236 patients), with results similar to the results presented. We restricted the analysis to persons with a baseline plasma HIV concentration >500 copies/mL (1967 patients) to reduce bias that might be associated with our inability to measure prior use of antiretroviral therapy from non-VA sources. The results were amplified: compared with persons with visits in all 4 quarters, the adjusted hazard ratio of death was 1.39 (95% CI, 1.03–1.88; $P = .03$), 2.05 (95% CI, 1.44–2.91; $P < .001$), and 2.21 (95% CI, 1.48–3.31; $P < .001$) for persons with visits in 3 quarters, 2 quarters, and 1 quarter, respectively. In this analysis, use of HAART rather than other antiretroviral therapy was significantly protective (adjusted hazard ratio, 0.75; 95% CI, 0.57–0.98; $P = .03$). Because there might have been variable time between the first antiretroviral prescription and the index visit, we performed analyses restricted to persons whose time between first prescription and index visit was ≤ 120 days. The results for these analyses were not meaningfully different from those presented.

DISCUSSION

In this cohort study of persons with HIV infection who were enrolled in care during the HAART era and who had a provider visit, a baseline laboratory assessment, and prescription of antiretroviral therapy, 36% were out of VA care for at least 3

Table 1. Baseline characteristics of a cohort of HIV-infected men who initiated antiretroviral therapy at a US Department of Veterans Affairs hospital or clinic, stratified by number of quarters in the first year during which an HIV primary care visit occurred.

Variable	All patients (n = 2619)	Patients with visits in 4 quarters (n = 1685)	Patients with visits in 3 quarters (n = 479)	Patients with visits in 2 quarters (n = 286)	Patients with visits in 1 quarter (n = 169)	P
Age, mean years (± SD)	44.5 (9.7)	45.5 (9.8)	43.2 (9.7)	42.3 (9.3)	42.4 (8.4)	<.001
Race						<.01
White	33.8	36.4	30.5	27.6	28.4	
Black	54.1	50.7	59.1	63.3	58.6	
Hispanic	8.2	8.6	7.7	5.6	10.1	
Other/unknown	3.9	4.4	2.7	3.5	3.0	
CD4 ⁺ cell count, median cells/L × 10 ⁶ (25th percentile, 75th percentile)	228 (81, 410)	212 (70, 393)	260 (100, 430)	256 (124, 452)	269 (115, 418)	<.001
Plasma HIV concentration, ^a median log ₁₀ copies/mL (25th percentile, 75th percentile)	4.58 (3.67, 5.17)	4.62 (3.68, 5.21)	4.46 (3.42, 5.09)	4.44 (3.66, 4.98)	4.56 (4.05, 5.04)	.02
HAART prescribed ^b	80.8	81.8	81.4	74.8	79.3	.05
Non-HIV-related comorbidity score						.06
≥2	5.8	6.7	5.4	1.8	5.3	
1	13.9	14.2	13.8	13.3	12.4	
0	80.3	79.2	80.8	85.0	82.3	
Hepatitis C virus coinfection	22.5	20.2	25.9	24.1	33.1	<.001
Alcohol abuse	24.5	21.3	25.9	34.3	36.1	<.001
Hard illicit drug use	20.7	17.1	23.8	29.7	33.1	<.001
Socioeconomic instability	28.3	27.4	28.0	32.2	31.4	.31

NOTE. Data are percentage of patients, unless otherwise indicated.

^a For all patients, n = 2236; for patients with visits in 4 quarters, n = 1452; for patients with visits in 3 quarters, n = 410; for patients with visits in 2 quarters, n = 235; and for patients with visits in 1 quarter, n = 139.

^b Defined as receipt of a protease inhibitor, a nonnucleoside reverse-transcriptase inhibitor, or a combination of zidovudine, lamivudine, and abacavir within 30 days of the first antiretroviral prescription.

months beginning in their first year of antiretroviral therapy. Approximately one-half of this 36% were out of care for at least 6 months. Patients out of care for as little as 3 months beginning in the first year of therapy had worse survival after adjusting for age, CD4⁺ cell count, plasma HIV concentration, hepatitis C virus coinfection, and other comorbid conditions. To our knowledge, this study is the first to demonstrate that poor retention in care for HIV infection (or, for that matter, for any chronic disease) has a negative impact on survival. The survival reduction associated with the poorest retention in care (i.e., associated with having a health care provider visit in only 1 of 4 quarters) was quite large, approaching that associated with having a baseline CD4⁺ cell count <200 × 10⁶ cells/L. Patients with poor retention in care also had less improvement in CD4⁺ cell count and plasma HIV concentration in response to antiretroviral therapy at 1 year.

The VA population is vulnerable and generally has few resources to buffer the consequences of lapses in care. Consequently, it is not surprising that interrupting VA outpatient care led to substantially worse survival in this study. Many other populations with HIV infection in the United States are similarly vulnerable, including clients dependent on the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act and Medicaid, which provide approximately one-half of the

HIV care in the United States [8, 18]. Furthermore, it is possible that similar relationships exist in other vulnerable populations, such as elderly individuals, persons receiving Medicaid, persons with multiple comorbidities, and the nearly 46 million Americans who do not have health insurance [19].

This study considered persons with adequate initial access to care, as indicated by their receipt of antiretroviral therapy. There are also problems earlier in the process of caring for HIV-infected patients. Approximately one-half of the patients who receive a diagnosis of HIV infection in the United States receive their diagnosis at an advanced stage of disease, which adversely affects their prognosis regardless of whether they receive HAART [20–22]. In a recent prospective study, 40% of persons with a recent diagnosis of HIV infection did not see a physician in the 6 months after diagnosis, and more than one-half of the patients were out of care within 1 year [23]. Similarly, in a retrospective study from a large clinic, nearly one-half of the patients entering care had large gaps in care beginning in the first year of treatment [4]. Thus, dramatic improvements in the outcomes of persons living with HIV infection could likely be realized if the disease stage at diagnosis and engagement and retention in HIV care could be improved [24].

HIV-infected patients who miss clinic visits may also miss taking their antiretroviral medications [25, 26]. Patients who

are poorly adherent to physician visits are less likely to receive HAART in the first place, are more likely to develop an infection with resistance to HAART, and are less likely to achieve HIV suppression [27–29]. Indeed, we constructed a measure of adherence to the initial antiretroviral therapy over the first 3 months of care [30] and found mean adherence percentages of 59%, 68%, 74%, and 79% in the groups with visits in 1, 2, 3, and 4 quarters, respectively ($P < .001$). We did not adjust for adherence to antiretroviral medication in the survival analyses, because it is likely that adherence or nonadherence to antiretroviral medication is on the causal pathway to the outcomes. Persons who are not retained in care cannot receive adherence-support interventions. The results of this study, even if largely driven by adherence to antiretroviral therapy, confirm that retention in care should be a goal of HIV care.

Reduced adherence to HAART, however, may not be the only important reason for high mortality among those with poor retention in care. Comorbid diseases other than HIV infection are common causes of disability and death, and they require active management [14, 31]. Worse outcomes in this cohort may well have been attributable to missed opportunities for treating substance use, psychiatric diseases, hepatitis C, diabetes, or heart disease, in addition to missed chances for antiretroviral therapy and prophylaxis against opportunistic infections. Because data on the cause of death are not available in these databases, we could not explore these possibilities.

The data from the present study provide objective support for HIV treatment guidelines that recommend that patients be seen every 3–4 months while receiving HAART [13]. They also confirm that policies and programs designed to improve retention in care, especially for those who are younger and less immunocompromised, are urgently needed. Little is known about how to retain patients in care. Provider continuity has been demonstrated to be important in general medical care [32]. Cross-sectional and nonrandomized studies of HIV-in-

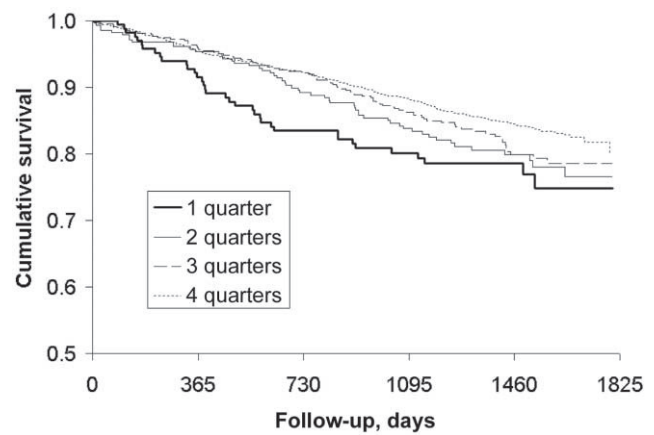


Figure 1. Kaplan-Meier plot of cumulative survival of the cohort, grouped by the number of quarters with an HIV primary care visit during the first year after the index visit ($P = .02$). Survival estimates begin 1 year after the index visit, because, by definition, all patients had to survive the first year.

ected persons in care have shown that case management, access to social services, and flexible clinic hours are associated with better retention [33–35]. One randomized prospective trial demonstrated that a case-management intervention at the time of diagnosis of HIV infection helped people to engage and remain in care, but even with the intervention, more than one-third of the patients were not retained in care for ≥ 1 year, and the intervention was not effective for crack cocaine users [23]. The high rates of interruption in care over 1 year observed in that study and the present study are alarming when one considers that patients with HIV infection must remain in care for many years or even decades. Further research is clearly needed.

This study has certain limitations. Because the study is based on observational data, residual bias may be present. Results of this study may not apply to women. Similar results might not

Table 2. Clinical outcomes 1 year after starting antiretroviral therapy in a cohort of HIV-infected men who initiated antiretroviral therapy at a US Department of Veterans Affairs hospital or clinic, stratified by number of quarters in the first year during which an HIV primary care visit occurred.

Outcome	All patients (<i>n</i> = 2619)	Patients with visits in 4 quarters (<i>n</i> = 1685)	Patients with visits in 3 quarters (<i>n</i> = 479)	Patients with visits in 2 quarters (<i>n</i> = 286)	Patients with visits in 1 quarter (<i>n</i> = 169)	<i>P</i>
CD4 ⁺ cell count change, median cells/ L $\times 10^6$ (25th percentile, 75th percentile) ^a	92.0 (10.0, 186.0)	100.0 (21.0, 191.0)	72.0 (2.0, 194.0)	20.0 (−73.0, 110.0)	48.5 (−7.5, 151.0)	<.001
Plasma HIV concentration change, median log ₁₀ copies/mL (25th percentile, 75th percentile) ^b	−1.29 (−2.38, −0.06)	−1.47 (−2.47, −0.22)	−0.90 (−2.08, 0)	−0.46 (−1.51, 0.14)	−0.22 (−1.36, 0.07)	<.001
Death after 1 year, % of patients	16.2	15.0	17.1	19.2	21.3	.06

^a Analysis was restricted to patients with both 1-year and baseline data available, as follows: all patients, 2066 (79%); patients with visits in 4 quarters, 1542 (92%); patients with visits in 3 quarters, 355 (74%); patients with visits in 2 quarters, 133 (47%); and patients with visits in 1 quarter, 36 (21%).

^b Analysis was restricted to patients with both 1-year and baseline data available, as follows: all patients, 1742 (67%); patients with visits in 4 quarters, 1312 (78%); patients with visits in 3 quarters, 304 (63%); patients with visits in 2 quarters, 102 (36%); and patients with visits in 1 quarter, 24 (14%).

Table 3. Results from a multivariate Cox regression model of death in a cohort of 2619 HIV-infected men who initiated antiretroviral therapy at a US Department of Veterans Affairs hospital or clinic.

Variable	Adjusted hazard ratio (95% CI)	P
No. of quarters with visit ^a		
1	1.94 (1.36–2.76)	<.001
2	1.68 (1.24–2.26)	<.001
3	1.41 (1.10–1.82)	<.01
4	1.00	
Baseline CD4 ⁺ cell count		
≤200 × 10 ⁶ cells/L	2.35 (1.82–3.05)	<.001
201–350 × 10 ⁶ cells/L	1.36 (0.99–1.87)	.06
>350 × 10 ⁶ cells/L	1.00	
Non-HIV-related comorbidity score		
≥2	2.00 (1.47–2.73)	<.001
1	1.62 (1.27–2.06)	<.001
0	1.00	
Hepatitis C virus coinfection	1.45 (1.16–1.82)	.001
Age, per 1-year increase	1.04 (1.03–1.05)	<.001

NOTE. Results were also adjusted for race/ethnicity (non-Hispanic black: adjusted hazard ratio [AHR], 1.16; 95% CI, 0.93–1.44; *P* = .20; Hispanic: AHR, 1.25; 95% CI, 0.87–1.80; *P* = .24; other/unknown: AHR, 0.87; 95% CI, 0.45–1.65; *P* = .66; non-Hispanic white: referent group), HAART versus other antiretroviral therapy (AHR, 0.86; 95% CI, 0.68–1.08; *P* = .20), alcohol abuse (AHR, 1.15; 95% CI, 0.87–1.52; *P* = .33), hard illicit drug use (AHR, 0.82; 95% CI, 0.60–1.12; *P* = .22), and socioeconomic instability (AHR, 1.06; 95% CI, 0.85–1.32; *P* = .63). HAART is defined as receipt of a protease inhibitor, a nonnucleoside reverse-transcriptase inhibitor, or a combination of zidovudine, lamivudine, and abacavir within 30 days of the first antiretroviral prescription.

^a No. of quarters in the first year after starting antiretroviral therapy during which an HIV primary care visit occurred.

have been found outside of the VA system. However, the VA has fewer financial barriers to care than many other safety net health care systems, so these results may represent a “best-case scenario” for the low-income, uninsured population within the United States. Use of non-VA resources is not captured in the database used in this study, although deaths are captured universally. Thus, the findings of the present study are likely to be conservative estimates of the effect of poor retention in care. A number of patients had missing CD4⁺ cell counts and could not be included in the study. This bias would also likely be conservative. We were unable to adjust for physician experience or other system factors that might influence survival [20, 36].

This study demonstrates that retention in care for HIV infection after starting antiretroviral therapy is often poor, even in a system with relatively few financial barriers to care. Patients with poor retention in care did not achieve the same CD4⁺ cell count, plasma HIV concentration, and survival benefits as those who were retained in care. Strategies to retain persons in long-term care need to be developed, tested, and implemented to maximize the benefit from currently available medical care.

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Potential conflicts of interest. All authors: no conflicts.

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