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Determinants of Survival for Native American Adults with HIV Infection

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ABSTRACT

Few if any Native American/Alaska Native (NA/AN) people have been included in highly active antiretroviral therapy (HAART) treatment trials or epidemiologic studies, leaving little data on which to be assured of the efficacy of HAART in this unique population. This study aims to evaluate the impact of HAART and review determinants of survival in a cohort of NA/AN persons receiving treatment for HIV in a real life clinical setting. A retrospective chart review of 235 HIV-infected Native Americans receiving services at an urban medical center operated by the Indian Health Service from January 1, 1981 through June 30, 2004 was conducted, providing 782.7 person-years of follow-up. The main outcome measures were time from study entry and from incident AIDS diagnosis to death. Death rates fell from 18.4 (13.3–25.4) per 100 person-years in the period prior to 1998 to 6.4 (4.6–8.8) per 100 person-years in the years 1998–2004, (RR 0.35, $p < 0.0001$). Factors associated with the greatest reduction in risk of death from time of study entry were current use of HAART, HR 0.13 (0.06–0.30, $p < 0.001$), and CD4 count ≥200 at entry, HR 0.16 (0.08–0.35, $p < 0.001$). Current use of HAART was the strongest predictor of survival from time of AIDS diagnosis, HR 0.11 (0.05–0.25, $p < 0.001$). The use of HAART therapy and CD4 count were primary predictors of survival. Earlier diagnosis and access to effective medical treatment will be key factors in reducing disparities in health brought about by HIV infection in Native American/Alaska Native communities.

INTRODUCTION

By 2003, a cumulative total of 3026 Native Americans and Alaska Native (NA/AN) people in the United States had been reported as diagnosed with the AIDS and an additional 1095 had been reported as infected with HIV.[1] AIDS incidence for NA/AN people during 2003 was estimated at 8.4 cases per 100,000 people per year, placing the incident rate in this population higher than in non-Hispanic white and Asian Pacific Islander populations, although lower than in African American and Hispanic populations.[1] HIV/AIDS is now the seventh leading cause of death in the 25- to 44-year-old age group of NA/AN.[2] Underreporting of HIV infection as a result of a variety of factors may lead to an underestimation of the prevalence and incidence of HIV infection and AIDS in NA/AN communities[3–5] and an underrecognition of the problem. Thus, while perhaps small in absolute number of cases compared to other populations, HIV/AIDS represents a significant burden of illness in native communities and will continue to have an impact within this population.[5]

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Morbidity and mortality from AIDS have decreased in the general United States and European populations, a fact largely attributed to the efficacy and availability of highly active antiretroviral therapy (HAART).[6–17] While there is no *a priori* reason to suspect that NA/AN people would not similarly benefit from treatment, few if any NA/AN people have been included in HAART treatment or epidemiologic studies,[18] leaving little data on which to be assured of the efficacy of HAART therapy in this population.

We sought to describe the rate of death and to identify the determinants of survival in a cohort of NA/AN people with HIV infection for whom information on treatment as well as disease status and comorbid conditions was available. Understanding HIV treatment efficacy in NA/AN people has implications on health care policy and practice as it relates to the goal of eliminating health disparities in the United States.

MATERIALS AND METHODS

Setting

The Phoenix Indian Medical Center (PIMC) is operated by the Indian Health Service (IHS), an agency of the United States Department of Health and Human Services. Eligible Native American and Alaska Native people receive the available health care services and prescription medications without direct out-of-pocket health care expense. This clinic provides care to people with HIV with a staff that includes family practice and internal medicine physicians, HIV case management, and pharmacy support. Services are coordinated with other Indian health system organizations and other AIDS service organizations through case management. When higher levels of care are required, clinical consultation is obtained through both public and private sector facilities.

Subjects

The study includes patients receiving services at Phoenix Indian Medical Center from January 1, 1981 through June 30, 2004. The medical center uses active surveillance of both diagnostic coding for health care encounters and results of laboratory testing to develop and maintain a registry of HIV patients. A total of 237 Native American HIV-infected patients were identified through the registry. Patients came from many regions of the southwestern United States. Patients were typically mobile, often traveling frequently between living situations in the Phoenix metropolitan area and rural reservation settings. All patients had provided consent for HIV testing and counseling and treatment within the context of delivery of clinical services. For purposes of performing this analysis, Institutional Review Board approval was obtained from the Phoenix Area Indian Health Service.

Data collection

Data were abstracted from written medical records, from HIV case management records, and from the electronic health information management system. These records included information on patient demographics, medications dispensed, laboratory tests, immunizations, hospital admissions, active medical problems, and purpose of visit for outpatient, inpatient and emergency care. We used the diagnoses of the attending physician as the basis for determining the presence of medical and behavioral conditions.

When required, additional information was obtained from the Arizona Department of Health Services HIV/AIDS Surveillance system. This system includes information on HIV and AIDS diagnosis dates, history of opportunistic infections, dates of death, and causes of death. This system receives reports as required by law from private and public health care providers throughout the state in an ongoing surveillance effort.

Definitions

Date of entry to the study was considered as the earliest known date at which a subject began receiving medical care for HIV at the Phoenix Indian Medical Center. Date of exit from the study was recorded as the latest date of three options: the last date of medical care or contact with the HIV case management nursing staff at Phoenix Indian Medical Center; the

date of the last available clinical information from the Arizona state surveillance database; or the date of death. Because of the mobility of the population and lack of access to surveillance data outside the state of Arizona, this censoring strategy was felt to reflect the most valid data available. Subjects were considered lost to follow-up if there had been no contact with the medical center or case management staff since January 1, 2004 (within 6 months of the start of this study), and data were censored to the last date of contact known.

CD4 counts, measured by flow cytometry, and HIV RNA viral load, measured by reverse transcriptase-polymerase chain reaction (RT-PCR), obtained within 3 months of diagnosis or entry to the study were recorded, excluding any measurements obtained after the start of antiretroviral therapy. AIDS was defined using the 1993 Centers for Disease Control (CDC) case definition.[19] HAART was defined as a regimen of three or more antiretroviral agents known to be active against HIV.[20]

Outcome measures

The primary outcome measures were the time from study entry and from an AIDS diagnosis to the time of death. Cause of death was abstracted from the medical record, from a death certificate, or from Arizona State HIV and AIDS surveillance records, including both HIV and non-HIV–related mortality.

Statistical analysis

Data analysis was performed using STATA 8.1 (Stata Corp., College Station, TX). All confidence intervals are presented at the 95% level. χ^2 or Fisher's exact tests were used to compare categorical variables, and analysis of variance (ANOVA) or Kruskall-Wallis testing was used for continuous variables. The survival analysis from time of AIDS to death included only the subset of patients with incident cases of AIDS since entry.

The study period was stratified into three time periods by calendar time: 1995 and prior reflecting the pre-HAART era, 1996–1997 reflecting the early HAART treatment era, and 1998 and beyond reflecting the late HAART treatment era.[12] Kaplan-Meier survival functions were generated, and the log-rank test was used to compare survival functions between different strata.

Cox proportional hazards regression was used to adjust for the effects of multiple variables, including age, gender, treatment era, CD4 count at entry/AIDS, viral load at entry/AIDS, type of AIDS defining event, use of HAART, use of protease inhibitors, use of prophylaxis for opportunistic infections, comorbid illness, and substance use. Regression models were generated in forward, stepwise fashion, including the strongest confounders first as determined by prior univariate analysis. The proportionality assumption of Cox models was tested using Schoenfeld residuals.

RESULTS

Demographic profile

There were 235 subjects for whom clinical data was available. Of these, 84 (36%) died, 109 (46%) were alive and had complete data up to the end of the study period, and 42 (18%) had data missing prior to the end of the period and therefore had data censored to the period of time for which data was available. The cohort contributed a total of 782.7 person-years of follow up time, ranging from a minimum of 1 day to a maximum of 14.1 years.

The mean age at entry was 34.7 years (standard deviation [SD] 8.7 years), ranging from 15.5 to 61.3 years. The study included 42 (17.9%) women and 193 (82.1%) men. There was no evidence for a change in the proportion of men and women enrolled by year of entry to the study ($p = 0.85$). There was no difference in median age at entry between men and women ($p = 0.42$).

For men, male-to-male sexual contact (MSM) was the primary risk factor for 69.6% (133 cases); followed by heterosexual contact, 13.1% (25 cases). A combination of MSM and injection drug use (IDU) accounted for 10.5% (20 cases) and IDU for 5.2% (10 cases). Heterosexual contact was the primary risk factor for HIV acquisition in women, 74.4% (29 cases); followed by IDU, 12.8% (5 cases); blood-borne contact, 10.3% (4 cases); and *in utero* transmission, 2.6% (1 case).

Prevalence of comorbid medical illness

Of the 213 subjects for whom detailed clinical records were available, 34 (16.0%) had diabetes mellitus and 49 (23.0%) had hypertension. Of the 183 subjects tested for hepatitis B, 47 (25.7%) had evidence of prior infection by serologic testing and 6 (3.3%) had chronic hepatitis B. Serologic evidence of prior hepatitis C infection was found in 46 (26.3%) of the 175 subjects tested, including 18 (10.3%) with chronic hepatitis C. Eighty-three (39%) subjects reported a history of depression and 27 (13%) had a history of a mental illness other than depression.

Laboratory measures of CD4 count

A CD4 count was available for 145 subjects at diagnosis and for 208 subjects at entry to care at PIMC. The median CD4 count at diagnosis was 259 interquartile range [IQR] 96–520), and the median CD4 count at entry was 249 (IQR 96–485). There was no evidence of variability in median CD4 count at diagnosis by year of diagnosis ($p = 0.20$) or in median CD4 count at entry by year of entry ($p = 0.29$). The median CD4 count at the time of an AIDS diagnosis was 132 (IQR 53–191). The median CD4 count at initiation of HAART therapy in this cohort was 196 (IQR 64–309). The overall median CD4 count at the time of death was 40 (IQR 9–156). For those dying of HIV-related causes, the median CD4 count at death was 17 (IQR 6–61) versus a median CD4 count of 376 (IQR 143–538) for those dying of non-HIV–related causes.

Use of antiretroviral therapy and prophylaxis for opportunistic infections

Of the 185 subjects with data available on pharmacologic drug use, 146 (78.9%) have used antiretrovirals at any time, 129 (70.1%) have used HAART at any time, and 107 (59.1%) are currently using HAART. Nearly half (99, 53.8%) have used protease inhibitors. For those with a history of AIDS, 81 (66.9%) are currently using HAART, and 80 (64.0%) have used a protease inhibitor during the course of treatment. For the 97 subjects with AIDS where prophylaxis is indicated, 86 (88.7%) are currently on appropriate prophylaxis.

AIDS-defining events

Data on AIDS defining events were available for 156 of the 160 subjects with AIDS. Eighty-two (52.6%) subjects had an AIDS diagnosis based on immunologic criteria alone (CD4 <200 or CD4 $< 14\%$) versus 74 (47.4%) who experienced one or more opportunistic infections (OI). *Pneumocystic carinii* pneumonia (PCP) (30 cases, 32.3%) was the most frequent event, followed by coccidiomycosis (11 cases, 11.8%), esophageal candidiasis (10 cases, 10.8%), AIDS wasting syndrome (6 cases, 6.5%), Kaposi's sarcoma (6 cases, 6.5%), and tuberculosis (5 cases, 5.4%). All other OIs occurred at a frequency of less than 5%.

Unique to this cohort was the high frequency of disease caused by coccidiomycosis. *Coccidiodes immitis* is a dimorphic fungus endemic in the soil of the Lower Sonoran Life Zone of the southwestern United States, Mexico, and Central and South America. Coccidiomycosis within the Native American populations of the Southwest has been well documented in the past,[21–23] as has the occurrence of coccidiomycosis within non-Native populations of HIV-infected persons living in coccidiodal endemic areas of Arizona.[24–26]

Rates of death

Death rates in the cohort declined after the introduction of HAART. Prior to 1998, the crude rate of death measured from study entry was

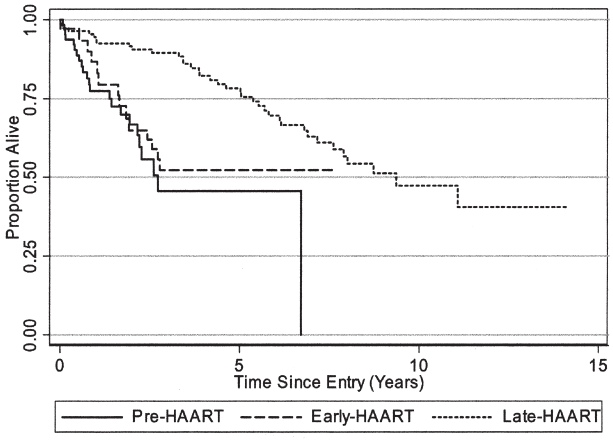

FIG. 1. Kaplan-Meier estimation of survival from entry adjusted for CD4 count. HAART, highly active antiretroviral therapy.

Table 1. Kaplan-Meier Estimates of Median Survival—Unadjusted

	Prior to 1998		*1998–2004*		*Overall*	
	Number of subjects	*Median survival (years)*	*Number of subjects*	*Median survival (years)*	*Number of subjects*	*Median survival (years)*
From HIV diagnosis	98	2.9 (2.2–6.2)	178	12.0 (7.2–13.4)	218	7.2 (5.6–9.1)
From entry to study	99	2.8 (2.3–*)	180	9.4 (7.2–*)	221	7.6 (6.1–11.1)
From incident AIDS	38	1.9 (1.2–2.7)	80	6.9 (4.4–*)	99	4.7 (3.4–6.9)

*Insufficient data points at longer time periods to calculate upper bound of confidence interval.

18.4 (13.3–25.4) per 100 person-years, declining to 6.4 (4.6–8.8) per 100 person-years in the years 1998–2004, (RR 0.35, $p < 0.0001$). Death rates from study entry ranged from 18.3 (13.8–24.2) per 100 person-years for those not on HAART, compared to 3.0 (1.8–5.0) per 100 person-years for those currently on HAART ($p < 0.0001$).

Survival analysis

Kaplan-Meier estimates of survival from entry were stratified by HAART era and adjusted for CD4 count (Fig. 1). There was no difference in survival from the pre-HAART to early-HAART eras ($p = 0.22$). Survival improved in the late-HAART time period ($p < 0.001$). A similar pattern was seen in survival from the time of incident AIDS diagnoses, with survival only improving in the late-HAART era (1998 and beyond).

Table 1 summarizes the median survival times from entry to the study, from HIV diagnosis, and from incident AIDS in the pre-1998 and post-1998 time periods (otherwise unadjusted). Median survival from entry improved from 2.8 years (2.3–*)[a] to 9.4 years (7.2–*), $p < 0.0001$. Median survival from the time of HIV diagnosis improved from 2.9 years (2.2–6.2) to 12.0 years (7.2–13.4), $p < 0.0001$. Median survival post0AIDS diagnosis improved from 1.9 years (1.2–2.7) to 6.9 (4.4–[a]) years, $p = 0.0001$.

Factors associated with survival from time of study entry are summarized in Table 2 based on the Cox proportional hazards regression analysis. There were a total of 192 subjects who had information available on potential confounding factors. They contributed 782.7 person-years of follow up and 55 deaths to the regression analysis. The current use of HAART therapy was associated with the greatest reduction in risk of death, HR 0.13 (95% confidence interval [CI] 0.06–0.30, $p < 0.001$). A CD4 count ≥200 at entry was also associated with a reduced risk of death, HR 0.16 (95% CI 0.08–0.35, $p < 0.001$), as was the use of protease inhibitors at any time during therapy, HR 0.37 (0.18–0.78, $p = 0.009$). However, it must be noted that protease inhibitor use was also strongly correlated ($r = 0.78$) with the past use of HAART, as the initial standard HAART regimens used in 1996–1997 included protease inhibitors. Having a diagnosis of AIDS during follow-up was associated with an increased risk of death, HR 4.10 (1.52–11.09, $p = 0.005$).

After controlling for treatment with HAART, CD4 count, and presence of AIDS, there was no independent association of survival with age at entry ($p = 0.65$), gender ($p = 0.97$), the use of prophylaxis for opportunistic infections ($p = 0.94$), diabetes ($p = 0.88$), hypertension ($p = 0.20$), hepatitis B ($p = 0.47$), hepatitis C ($p = 0.14$), depression ($p = 0.85$), or mental illness ($p = 0.34$; p values derived by likelihood ratio tests). The effect of HAART use accounted for the initial association of calendar time with survival. Additionally, there was no association of survival with past or present substance abuse, including IDU, other drug use, alcohol use, and tobacco use. No association was found between survival and viral load measured at entry ($p = 0.51$) or AIDS-defining event ($p = 0.11$), although smaller numbers of subjects with available data limited the strength of both of these analyses.

There were 42 deaths among the 100 persons with an incident case of AIDS. A total of 87 of these subjects with 32 deaths had adequate in-

[a]* = Insufficient data at longer follow-up periods to calculate upper bound of confidence interval.

Table 2. Hazard Ratios for Survival from Time of Entry

	HR	*95% CI*	p *value*
HAART era			
Pre	1.0	"–"	"–"
Early	2.23	0.97–5.11	0.06
Late	0.87	0.36–2.08	0.75
HAART Use—Current	0.13	0.06–0.30	< 0.001
CD4 Count			
< 200	1.0	"–"	"–"
≥ 200	0.16	0.08–0.35	< 0.001
Protease inhibitor use	0.37	0.18–0.78	0.009
Presence of AIDS	4.10	1.52–11.09	0.005

HAART, highly active antiretroviral therapy.

formation for inclusion in the regression model (266.2 person-years of follow-up). During analysis of survival from an incident case of AIDS, an additional time period at year 2002 was added to the Cox regression in order to satisfy proportionality constraints.

Current use of HAART was again the strongest predictor of improved survival, HR 0.11 (0.05–0.25, $p \leq 0.001$; Table 3). There was no strong evidence for an independent effect of CD4 count measured at the time of AIDS on survival ($p = 0.14$). There was no independent effect of protease inhibitor use ($p = 0.25$), use of prophylaxis ($p = 0.18$), age at the time of AIDS diagnosis ($p = 0.47$), gender ($p = 0.75$), diabetes ($p = 0.25$), hypertension ($p = 0.09$), depression ($p = 0.48$), or mental illness ($p = 0.78$). A limited number of events constrained the ability to detect an independent effect of viral hepatitis on survival. Among the 59 subjects with data available on severity of AIDS-defining event, there was some evidence for the most severe AIDS defining events being associated with poorer survival, HR 8.81 (1.59–49.0, $p = 0.04$). There was no association of survival with past or present substance abuse once use of HAART and CD4 count were controlled for. For the subset where viral load at AIDS diagnosis was known ($n = 59$, deaths = 13), there was no association between viral load at AIDS and survival ($p = 0.60$).

DISCUSSION

We have described a dramatic decline in the rate of death in this population of HIV-infected NA/AN patients in a pattern similar to other populations where the introduction of highly active antiretroviral therapy has had profound effects on morbidity and mortality.[11–16,27–29] The use of HAART therapy and CD4 count were found to be the main predictors of survival. These data suggest that earlier diagnosis and access to effective medical treatment will be key factors in reducing the disparities in health brought about by HIV infection in native communities.

We found that death rates fell from 18.4 (13.3–25.4) per 100 person-years in the period prior to 1998 to 6.4 (4.6–8.8) per 100 person-years in the years 1998–2004, (RR 0.35, $p < 0.0001$), a decline of 288%. For comparison, mortality rates in a large U.S. cohort fell from 20.2 per 100 person-years in 1994 to 8.4 per 100 person-years in 1998.[27] In the collaborative EuroSIDA study, overall mortality rates declined from 19.0 (17.7–20.3) per 100 person-years in the pre-1996 era, to 9.3 (8.6–10.0) per 100 person-years in 1996–1997, to 2.6 (2.4–2.8) per 100

Table 3. Hazard Ratios for Survival from Incident AIDS

	HR	*CI*	p *value*
HAART era			
Pre	1.0	"–"	"–"
1996–1997	1.51	0.57–4.00	0.41
1998–2002	0.26	0.08–0.78	0.02
> 2002	0.5	0.17–1.41	0.19
HAART Use—Current	0.11	0.05–0.25	< 0.001
AIDS event			
Severe vs. all others	8.81	1.59–49.0	0.04

HAART, highly active antiretroviral therapy.

person-years in 1998 and beyond.[12] Mortality rates in other large cohorts remain quite low, with the Antiretroviral Cohort Collaboration reporting mortality rates in patients newly starting HAART of 1.42 per 100 person-years. Despite improvements, mortality rates in this cohort of Native American patients remain slightly above those reported in other large cohort studies, although this comparison does not account for potential differences in HIV stage at entry to these different cohorts.

Additionally, this population may be at particular risk for decreased adherence to HAART therapy. As reported in the 2000–2001 Trends in Indian Health, 31.6% of AI/AN live below the poverty line versus 13.1% of the general population.[2] In a survey of Native Americans seeking care for HIV/AIDS in a rural southwestern region of the United States, 32% lacked permanent housing, 68% lacked transportation, and 43% had no telephone. Access to needed services such as housing assistance, transportation, mental health services, and substance abuse services often went unmet.[30] Although this represents only a sample of NA/AN individuals with HIV, it does reflect the complex medical, economic, and social needs of these patients. Future studies should include direct measures of medication adherence, assess barriers to adherence, and assess potential medication related side effects of therapy in this population. Despite the challenges of delivering care and maintaining adherence, those patients on HAART therapy have had remarkable improvements in survival.

The main determinants of survival were the use of HAART therapy and CD4 count that is consistent with survival determinants from other populations.[27,31] Current use of HAART therapy resulted in a sevenfold to eightfold decline in risk of death. Because of relatively small number of cases, it was difficult to detect an independent effect of protease inhibitors, viral load, and the use of prophylaxis, although these factors have been associated with improved survival in the era of antiretroviral therapy.[31–34] Once accounting for use of HAART and CD4 count, no independent association between comorbid medical illness or substance abuse and survival was found. Again, increased case numbers would have strengthened the ability to detect an effect.

This cohort presented for care at relatively advanced stages of disease, with 21% of patients having an opportunistic infection at the time of diagnosis. At the time of entry 41% already had a CD4 count below 200, and the median CD4 count at initiation of HAART therapy was 196 (IQR 64–309). Poorer outcomes are associated with initiating HAART therapy below a CD4 count of 200[35] and with a prior history of opportunistic infection.[27] These facts underscore the importance of assuring access to both treatment and testing and counseling services.

Our study has several limitations. The retrospective nature of this study placed limitations on access to original data and on detailed follow-up of subjects. The present cohort of patients also reflects a sero-prevalent cohort, where the date of true seroconversion is unknown. While adjusting for factors such as CD4 count at entry, our study may not fully account for all factors present at the time of initial and early infection that may impact survival. Because of this, one cannot conclude that overall survival in this cohort of Native Americans is better or worse than other groups in the United States and elsewhere, but only that they appear to have higher rates of death from the time at which they present for care in relation to other cohorts studied during a similar time period.

Overall, 42 of 235 (18%) of the cohort was lost to follow-up. Those lost to follow-up we more likely to be younger (mean age 28.9 years versus 36.2 years, $p = 0.0001$) and to have a higher CD4 count at entry (median CD4 506 versus 267, $p = 0.004$). While just as likely to have a diagnosis of AIDS ($p = 0.17$), they were less likely to have ever been on HAART therapy (55.9% versus 79.6%, $p = 0.006$). There was a marked difference in the prevalence of active use of drugs (30.0% versus 6.4%, $p < 0.001$). These patients lost to follow-up may be at higher risk of adverse outcomes because of difficulties with adherence to care and treatment.

Finally, it may not be possible to generalize our findings to all NA/AN people with HIV. Native Americans and Alaska Natives represent a very diverse group of over 557 federally recognized tribes and nations living in various

regions of the United States.[5] This cohort composes only those who are seeking care at one health center in the southwestern United States.

Research on treatment-seeking behavior, HIV risk awareness, and barriers to testing and treatment are essential to improving early testing and treatment rates and to designing educational campaigns in hopes of improving clinical outcomes in this population. A larger collaborative study of Native American patients with HIV and continued follow up in this cohort could add important information on the course of disease in this unique group. NA/AN people with HIV face significant social and comorbid conditions that could represent barriers to the effectiveness of HAART therapy in actual clinical settings.

Future studies should include measures of the complex medical, economic, and social issues affecting NA/AN patients so as to be able to better understand how these factors influence outcomes. This study was performed at one of the largest medical centers in the IHS where highly skilled medical, nursing, behavioral, case management, and pharmacy staff were available and where resources were expended to deliver HAART therapy. Access to this level of care may not be available to all NA/AN people with HIV in smaller IHS facilities or where no IHS facilities exist. Future studies should therefore include measures of access to and the quality of these services.

In light of the dramatic improvement in mortality associated with the use of HAART in this cohort, early diagnosis and access to care that promotes initiation and adherence to appropriate therapy must be priorities. The IHS must assure, through policy and practice, that such services are available whether as a result of assuring competent care anywhere within the system or through partnership with programs capable of providing such services. Communities must advocate for education and for inclusion of culturally acceptable services and acceptance within communities to increase the likelihood of testing and counseling. Finally, local, regional, and state partnerships must be strong to ensure inclusion in surveillance activities.

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