

Differences in Prescription of Antiretroviral Therapy in a Large Cohort of HIV-Infected Patients

*A. D. McNaghten, *Debra L. Hanson, *†Mark S. Dworkin, *Jeffrey L. Jones, and
the Adult/Adolescent Spectrum of HIV Disease Group

**Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia, U.S.A. †Present affiliation for Mark S. Dworkin: Illinois Department of Public Health, Chicago, Illinois, U.S.A.*

Summary: The objective of this study was to determine factors associated with prescription of highly active antiretroviral therapy (HAART). The authors observed 9530 patients eligible for antiretroviral therapy (ART) in more than 100 hospitals and clinics in 10 US cities. Multiple logistic regression analysis was used to assess factors associated with HAART prescription, stratifying patients by no history versus history of ART to assess the association between prescription and CD4, viral load, and outpatient visits. Overall, female gender (odds ratio [OR], 0.68; 95% confidence interval [CI], 0.60–0.76) and alcoholism (OR, 0.85; 95% CI, 0.74–0.99) were associated with decreased likelihood of HAART prescription. Enrollment at a private facility (OR, 1.33; 95% CI, 1.14–1.56), heterosexual exposure (OR, 1.34; 95% CI, 1.13–1.58), and Hispanic ethnicity (OR, 1.19; 95% CI, 1.04–1.37) were associated with prescription. For patients with no history of prescribed ART, CD4 <500 cells/ μ L (OR, 3.94; 95% CI, 2.02–7.66), and high viral load were associated with increased likelihood of prescription; for patients with history of ART prescription, those whose outpatient visits averaged ≥ 2 per 6-month interval (OR, 1.30; 95% CI, 1.10–1.54) were more likely and those with high viral load were less likely to be prescribed HAART (OR, 0.50; 95% CI, 0.44–0.56). The authors found differences in HAART prescription by gender, race, exposure mode, alcoholism, and provider type for all patients, by CD4 and viral load for patients with no history of ART prescription, and by average number of outpatient visits and viral load for patients with history of ART prescription. **Key Words:** Highly active antiretroviral therapy (HAART)—Antiretroviral therapy—HAART prescription.

The use of highly active antiretroviral therapy (HAART) has been associated with decreasing AIDS incidence and AIDS-related deaths in the United States since 1996 (1,2) and has been shown to decrease the risk of death for persons with AIDS (3,5). Although the ability of HAART to decrease plasma HIV RNA levels and increase CD4 T-lymphocyte counts in persons infected with HIV has been demonstrated (6,7), not all persons

who meet the criteria for antiretroviral therapy (ART) are prescribed HAART.

Poor adherence to protease inhibitor (PI)-containing HAART may result in viral cross-resistance to PIs (8,9) and the emergence of drug-resistant strains of HIV (9–11). Factors such as alcohol or drug abuse, mental health status, and infrequent outpatient care may influence HAART prescription; for example, providers have reportedly been less likely or slower to prescribe HAART to injection drug users (IDUs) (4,12–14) and patients diagnosed with depression (14). To further reduce morbidity and mortality associated with HIV and AIDS in the United States, it is important to determine which

Address correspondence and reprints to A. D. McNaghten, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mail Stop E47, Atlanta, GA 30333, U.S.A.; e-mail: mcnaghtena@zimdcdc.co.zw
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groups are least likely to be prescribed HAART so they can be provided services to assist with obtaining and adhering to treatment. We studied factors associated with HAART prescription and determined the proportion of patients who met the criteria for ART according to guidelines and recommendations (15,16) at the time of observation and for whom HAART was prescribed.

METHODS

Data analyzed were from the Centers for Disease Control and Prevention's Adult/Adolescent Spectrum of HIV Disease (ASD) project. ASD is a multicenter medical record review surveillance project in selected medical facilities in Atlanta, Dallas, Denver, Detroit, Houston, Los Angeles, New Orleans, New York City, Bayamon (Puerto Rico), San Antonio, and Seattle. HIV-infected persons aged ≥ 13 years who attend participating clinics are eligible for enrollment in ASD. The methods used in ASD have been previously described (17,18). Medical records of ASD participants are reviewed for the 12 months before their enrollment date and at subsequent 6-month intervals until death or loss to follow-up. Information collected includes basic demographics, mode of HIV exposure, prescription of antiretroviral and other medications, CD4 T-lymphocyte counts, HIV RNA viral load, complete history of AIDS-defining opportunistic illnesses (OIs), other infections, and other conditions and behaviors of medical importance (19).

To assess the prescription of recommended HAART (15,16,20,21), analyses were limited to data collected from patients who had a 6-month follow-up interval that included at least one inpatient or outpatient visit during 1999 (observation interval). Patients whose observation interval covered 3 or more months during 1999 were also included; therefore, total observation time was October 1998 through March 2000. Patients were eligible for inclusion in the analysis if before the observation interval they had an AIDS OI diagnosis, a CD4 count of < 500 cells/ μL , or HIV RNA viral load $> 20,000$ copies/mL reverse transcriptase-polymerase chain reaction (RT-PCR) or $> 10,000$ copies/mL branched chain deoxyribonucleic acid (bDNA), any of which would warrant HAART according to guidelines in effect during this time.

For these analyses, we defined HAART as prescription of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and either a PI or a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) as recommended by the *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (15,16) and the recommendations of the International AIDS Society-USA panel (20,21). We also included HAART regimens that were prescribed during the study period before they were officially recommended in 2000 and 2001 (22,23). If ART medications were prescribed in addition to recommended regimens, the patient was still classified as receiving HAART. ART was defined as any antiretroviral medication prescribed alone or in combination with other antiretroviral drugs. ASD collects information on medications prescribed during a 6-month interval. For patients prescribed more than one ART regimen during an interval, we used the first regimen prescribed. High viral load was defined as HIV RNA of $> 20,000$ copies/mL (RT-PCR) or $> 10,000$ copies/mL (bDNA), and low viral load was defined as $\leq 20,000$ copies/mL (RT-PCR) or $\leq 10,000$ copies/mL (bDNA).

We examined frequencies of covariates by HAART use, followed by logistic multiple regression analysis to assess factors associated with HAART prescription. The multivariate regression model included the following covariates: private or public facility; site; mode of HIV exposure, race, sex, and age at the beginning of the observation interval;

current alcoholism (current defined as during the previous or observation interval); and current dementia, depression, or psychosis. Alcoholism, depression, and psychosis were recorded if documented in the patient's medical record; ASD sites do not use standard criteria for diagnosing these conditions. The following covariates were stratified by no history of ART prescription versus history of ART prescription since enrollment in ASD: average number of outpatient visits per interval before the observation interval, most recent CD4 count in the interval before the observation interval, and most recent viral load in the interval before the observation interval. The term "no history of ART prescription" in this analysis refers to patients who were not prescribed ART after enrollment in ASD and in any interval before the observation interval; prescription of ART before enrollment in ASD is not known for all patients. We computed odds ratios (ORs) and 95% confidence intervals (CIs). Two-way interactions of sex and other covariates in the model were studied.

RESULTS

Our analysis included 9530 patients eligible for ART (15,16,22,23) who had at least one inpatient or outpatient visit during an observation interval that included time observed in 1999; 10.1% had an average of ≤ 1 outpatient visit per interval, and 89.9% had an average of 2 outpatient visits per interval. Of these patients, 26.7% were female, 46.2% black, 31.4% white, and 20.5% Hispanic (Table 1). Mode of exposure to HIV was known for 80.7% of patients; the largest exposure group was men who had sex with men (MSM), followed by IDUs, and those exposed through heterosexual contact. Current alcoholism was recorded for 9.4% of patients. Current dementia was recorded for 0.9% of patients, current psychosis for 4.7%, and current depression for 17.4%.

Of the total, 57.2% of patients were prescribed HAART, 79.4% were prescribed ART, and 20.6% were not prescribed ART. Among patients with a history of ART prescription, 60.1% were prescribed HAART during the observation interval. Of patients with no history of ART prescription, 27.9% were prescribed HAART during the observation interval.

The proportion of male patients prescribed HAART was larger than the proportion of female patients (Table 1). Half of IDUs and fewer than half of persons with a current diagnosis of alcoholism or psychosis were prescribed HAART.

In the multivariate analysis, among all persons, female gender and alcoholism were associated with decreased odds of HAART prescription compared with male gender and no alcoholism, respectively. Factors associated with HAART prescription included ASD enrollment at a private facility compared with a public facility, heterosexual contact as mode of exposure compared with MSM, and Hispanic ethnicity compared with white race. For patients with no history of ART prescription, patients with a CD4 count < 500 cells/ μL compared with those

TABLE 1. Factors associated with highly active antiretroviral therapy (HAART) prescription

Characteristic	% of all patients (N = 9530)	% of patients prescribed HAART (n = 5456)	Odds ratio (95% CI) ^a
Race/ethnicity	100.0	57.2	
White	31.4	57.4	Reference
Black	46.2	54.7	1.03 (0.92–1.14)
Hispanic	20.5	62.6	1.19 (1.04–1.37)
Asian/Pacific Islander	1.1	62.4	0.92 (0.60–1.40)
American Indian/Alaska Native	0.6	51.8	0.93 (0.53–1.62)
Sex			
Male	73.3	58.8	Reference
Female	26.7	52.9	0.68 (0.60–0.76)
Age (years)			
≥25	96.8	57.4	Reference
<25	3.2	52.6	0.89 (0.70–1.13)
Mode of HIV transmission			
Male-to-male sex	41.0	59.6	Reference
Hemophilia	0.3	74.2	1.72 (0.74–3.98)
Heterosexual contact	13.4	59.0	1.34 (1.13–1.58)
Injection drug use and male to male sex and injection drug use	24.3	50.4	0.90 (0.80–1.02)
Transfusion recipient	1.7	61.2	1.31 (0.92–1.87)
Other/risk not reported	19.3	59.0	1.26 (1.10–1.45)
Current clinical diagnoses ^b			
Psychosis	4.7	47.6	0.84 (0.68–1.03)
Depression	17.4	56.1	0.98 (0.88–1.10)
Dementia	0.9	54.3	0.88 (0.56–1.38)
Alcoholism	9.4	48.3	0.85 (0.74–0.99)
Facility type at enrollment			
Public	90.2	56.5	Reference
Private	9.8	64.6	1.33 (1.14–1.56)
No history of ART prescription ^c	(n = 843)	(n = 235)	
CD4+ T-lymphocyte count			
≥500	12.6	11.3	Reference
0–499	42.9	38.1	3.94 (2.02–7.66)
Missing	44.5	22.7	1.06 (0.50–2.25)
HIV RNA level			
≤10k (bDNA) or ≤20k (RT-PCR)	21.5	16.6	Reference
>10k (bDNA) or >20k (RT-PCR)	25.9	32.6	2.12 (1.27–3.56)
Missing	52.7	30.2	3.67 (2.06–6.54)
Outpatient visits			
<2 average/interval	33.9	31.1	Reference
≥2 average/interval	66.1	26.2	0.97 (0.66–1.40)
History of ART prescription ^c	(n = 5221)	(n = 8687)	
CD4+ T-lymphocyte count			
≥500	68.1	15.9	Reference
0–499	63.0	57.0	0.93 (0.83–1.08)
Missing	49.3	27.0	0.71 (0.60–0.84)
HIV RNA level			
≤10k (bDNA) or ≤20k (RT-PCR)	69.1	53.0	Reference
>10k (bDNA) or >20k (RT-PCR)	51.9	20.6	0.50 (0.44–0.56)
Missing	48.4	26.5	0.57 (0.49–0.65)
Outpatient visits			
<2 average/interval	46.5	7.8	Reference
≥2 average/interval	61.3	92.2	1.30 (1.10–1.54)

HAART, highly active antiretroviral therapy; CI, confidence interval; RT-PCR, reverse transcriptase polymerase chain reaction; bDNA, branched chain deoxyribonucleic acid.

^a Odds ratios are from a multiple logistic regression including all the covariates.

^b Reference is absence of condition or behavior in the interval prior and the interval of observation; conditions and behaviors are not mutually exclusive.

^c CD4 counts, viral load, and number of outpatient visits were assessed in a multiple logistic regression model stratified by no history of ART prescription versus history of ART prescription from time of enrollment in ASD to the interval prior to the observation interval.

with a CD4 count of ≥ 500 cells/ μ L, and patients with high viral load compared with those with low viral load had an increased likelihood of HAART prescription. For patients with a history of ART prescription, those whose outpatient visits averaged ≥ 2 times per 6-month interval were more likely to be prescribed HAART compared with those whose visits averaged < 2 per 6-month interval, and patients with high viral load were less likely to be prescribed HAART compared with those with low viral load. There were no significant two-way interactions between sex and other covariates in the model.

Of the 10 most commonly prescribed ART regimens, 8 met the definition of HAART (Table 2). Two dual-combination therapy regimens (non-HAART)—zidovudine (ZDV) + lamivudine (3TC), and stavudine (d4T) + 3TC—were prescribed for 4.5% and 2.9% of patients prescribed ART, respectively. These 10 most commonly prescribed regimens represent 54.9% of all prescribed ART regimens.

DISCUSSION

Our finding that female gender was associated with a decreased likelihood of HAART prescription differed from the finding of Palella et al. (4) that PI prescription did not significantly differ by sex, but it supports the findings of studies of smaller numbers of patients. Stone et al. (24), who examined prescription of HAART by demographic characteristics among 248 patients with HIV/AIDS in care in Rhode Island, found that women were less likely to be prescribed PI-containing HAART regimens than men. Andersen et al. (25) reported that among 2864 patients in the HIV Cost and Services Utilization study during 1996 and early 1997, female drug users were one third as likely as homosexual men to receive HAART early. Smith and Kirking (26) reported that among 1586 HIV-infected persons interviewed for

the AIDS Cost and Utilization Survey during 1991 and 1992, female gender was associated with being less likely to use ART. Female gender may be associated with lack of access to insurance and medical care, which may decrease the likelihood of HAART prescription. We could not assess whether patient refusal of ART may have contributed to the decreased likelihood of HAART prescription for women, or whether decreased access to HAART as a result of poorer socioeconomic status, insurance, or similar factors contributed to this finding because ASD data do not include the reason a medication is not prescribed. In an earlier analysis of ASD data, Blair et al. (27) found that women had lower viral load levels than men with the same CD4 counts. Although we controlled for viral load in our analysis, HAART prescription may be delayed for some women on the basis of measures of viral load.

In our study, alcoholism was associated with decreased odds of HAART prescription. Study patients with current alcoholism may not be prescribed HAART because of physicians' concerns about adherence. Persons who chronically abuse alcohol may experience impaired cognition, lack of inhibition, and blackouts (28), which may result in decreased adherence.

In our study, as in others (29,30), patients who received care at a private facility had an increased likelihood of HAART prescription. For example, Odem et al. (29) found that women who received HIV care at a private facility were seven times more likely to report being prescribed a PI than women who received care at a public facility. Although some patients were enrolled in ASD at a private facility, care may have been received at private and public facilities or solely at a public facility after enrollment.

Patients with heterosexual contact as their mode of HIV exposure were more likely than MSM to be prescribed HAART. Junghans et al. (13) found that heterosexual patients were slower than MSM to initiate HAART, and Stone et al. (24) found that patients exposed through heterosexual contact were significantly less likely to be prescribed PIs. Mocroft et al. (12) found no significant differences in HAART initiation for heterosexual patients compared with homosexual patients.

According to several studies, blacks and Hispanics were less likely to be prescribed PIs (24,29) and HAART (25). However, in our analysis, Hispanic ethnicity, compared with white race, was significantly associated with an increased likelihood of HAART prescription. Sorvillo et al. (30) found that blacks were less likely to be prescribed PIs than whites and US-born Latinos; Smith and Kirking (26) reported that black race was associated with being more likely to use ART. In our analysis, black race

TABLE 2. Ten most commonly prescribed ART regimens among patients prescribed antiretroviral therapy during 1999 ($n = 7568$)

ART regimen	Patients	
	Number	%
d4T + 3TC + nelfinavir	866	11.4
ZDV + 3TC + nelfinavir	838	11.1
ZDV + 3TC + indinavir	543	7.2
d4T + 3TC + indinavir	488	6.5
ZDV + 3TC	342	4.5
d4T + ddI + nelfinavir	262	3.5
d4T + 3TC + nevirapine	217	2.9
d4T + 3TC	217	2.9
ZDV + 3TC + nevirapine	209	2.8
ZDV + 3TC + efavirenz	175	2.3

d4T, stavudine; 3TC, lamivudine; ZDV, zidovudine; ddI, didanosine.

was not a significant predictor of the prescription of HAART. However, in an ASD analysis of factors associated with HAART prescription in 1998, black race compared with white race was significantly associated with a decreased likelihood of HAART prescription (31). Differences by race may be attenuated in our study because ASD participants are in care. Population-based data should be used to investigate differences in HAART prescription by gender and race.

Among patients with no history of ART prescription, low CD4 count and high viral load were associated with an increased likelihood of HAART prescription, a finding that is consistent with the antiretroviral treatment guidelines (15). Among patients with a history of HAART prescription, patients averaging ≥ 2 outpatient office visits per 6-month interval were more likely to be prescribed HAART. Patients who interact with their health care provider more than once every 6 months have more opportunities to be prescribed HAART, may make regular visits to continue HAART prescription, and may be considered more likely to adhere to treatment regimens. Some patients with >2 visits every 6 months may have been symptomatic or in more advanced stages of HIV disease, increasing the likelihood of HAART prescription. The association between high viral load and decreased likelihood of HAART prescription among patients with a history of ART prescription is likely due to the fact that patients in late stages of disease or for whom HAART is failing may discontinue therapy. The large proportions of patients with a history of ART prescription with CD4 counts of ≥ 500 cells/ μL (68.1%) and low viral load (69.1%) and for whom HAART was prescribed likely reflect the effect of HAART.

CD4 counts and HIV RNA level were missing for 44.5% and 52.7%, respectively, of patients with no history of ART prescription and for 27% and 26.5%, respectively, of patients previously prescribed HAART. Among patients with a history of ART prescription, missing CD4 and missing viral load were significantly associated with a decreased likelihood of HAART prescription, and missing viral load was associated with an increased likelihood of prescription among patients with no history of ART prescription. These patients likely represent a range of immunologic and virologic statuses, making it difficult to speculate how these missing laboratory values would affect the results. If these patients had fewer outpatient visits, this would likely decrease their opportunities for both laboratory tests to be conducted and any type of ART to be prescribed.

Injection drug use and current psychosis, dementia, and depression were not associated with HAART prescription. These conditions were hypothesized to be fac-

tors associated with the lack of prescription of HAART for ASD study patients because of possible concerns about adherence among prescribing physicians. According to an analysis of the ASD data using a similar model for patients in care in 1998, similar to other studies, IDUs were less likely than MSM to be prescribed HAART (31). Mocroft et al. (12) found that among patients in the EuroSIDA Study Group, IDUs were 27% less likely to start HAART compared with homosexual men. Similarly, Junghans et al. (13) reported that IDUs were slower to initiate HAART compared with MSM, and Fairfield et al. (14) found that injection drug use, compared with the absence of such use, was associated with delayed initiation of PIs. Palella et al. (4) reported that IDUs were less likely than other patients in their study to receive PIs. Persons who experience hallucinations, delusions, and distorted reality characteristic of psychosis (32,33) may not be able to adhere to HAART. Depression (34), depressive symptoms (35,36), and injection drug use (34,37) have been associated with decreased adherence to ART. Because lack of adherence to PI-containing regimens can result in drug-resistant strains of HIV (9–11), providers may delay prescribing HAART for some patients who are asymptomatic to avoid decreased effectiveness of a later HAART regimen that contains a PI (8,11). In addition, HIV that is resistant to PIs can be transmitted to others, which may decrease the effectiveness of PIs and HAART in newly infected persons (38–41). The *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* states that patients should not be excluded from receiving ART on the basis of behaviors or conditions that one may assume may induce nonadherence (15). Before prescribing complex medication regimens, providers should discuss adherence with patients.

In our study, 57.2% of all persons eligible for ART under the current guidelines (15) were prescribed HAART in 1999. We conclude that significant gaps may remain in ensuring the standard of care is available for eligible patients. Determining the barriers to the standard of care would require additional data such as treatment failure, adherence, side effects of therapy, provider knowledge of the standard of care, provider practices, and access to health care, therapies, and insurance. Programs to improve access to ART, combined with progress in treatment and improvements in access to care and adherence, should further improve the health and survival of persons living with HIV and AIDS. Case management, the AIDS Drug Assistance Program, directly observed therapy, referrals to mental health services, substance abuse treatment, and other social services may be essential to sustain the benefits of HAART.

Our study did have limitations. Patients “not prescribed ART” in this analysis were those not prescribed ART during time observed in the ASD study and may include patients prescribed ART prior to enrollment in ASD. If patients classified as “not prescribed ART” were actually receiving ART, differences between those with no history of ART prescription and those with a history of ART prescription would be minimized, resulting in a conservative representation of the differences between the two groups. To examine the association between the covariates and HAART prescription, only the first regimen prescribed in the observation interval was considered, minimally underestimating the number of patients prescribed HAART during the study period. Diagnoses such as depression and alcoholism were subject to physician interpretation. No standardized methods or criteria were used to diagnose these conditions, and some physicians or study sites may use these diagnoses more often than others. Only a notation of depression and alcoholism in a patient’s medical record was available in the ASD study. Kessler et al. (42) estimated the 12-month prevalence of various psychiatric disorders from the National Comorbidity Survey. A major depressive episode during the past 12 months was reported by 10.3%, which is lower than the 17.4% with a diagnosis of depression in our study. Rates of alcoholism similar to those for ASD participants (9.4%) have been reported for the general population. According to Grant et al. (43), 7.4% of Americans meet the diagnostic criteria for alcoholism or alcohol abuse.

The most commonly prescribed HAART regimens consisted of two NRTIs and a PI. The benefits of decreased morbidity and mortality from dual therapy with two NRTIs have been demonstrated (3,44,45). Although therapy consisting of two NRTIs does not as consistently suppress plasma HIV below detectable levels as does triple therapy with two NRTIs and a PI (15), 583 patients at ASD health care facilities were still being prescribed dual-therapy regimens during 1999 (15). Patients may be prescribed dual therapy instead of HAART because of cost, previous adverse effects, the decision to save exposure to PIs until virologic failure occurs, or satisfaction with the effectiveness of the dual therapy. Suh et al. (46) reported that patients declined HAART due to fear of side effects, denial of their medical condition, or negative feedback regarding HAART from others.

Our results demonstrate apparent differences by gender, race, mode of exposure to HIV, diagnosis of alcoholism, and provider type for all patients, by CD4 count and viral load for patients with no history of ART prescription, and by the average number of outpatient visits

and viral load for patients with a history of ART prescription. Patients with psychological conditions, such as psychosis and depression, and those who inject drugs or abuse alcohol must be judged patient by patient to determine whether the condition may lead to nonadherence to HAART. Each of these differences deserves further study to determine whether factors such as access to ART, patient or provider preferences, or health care providers’ perceptions of which groups are more likely to adhere to HAART regimens could increase the prescription of HAART for these populations.

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APPENDIX

Adult/Adolescent Spectrum of HIV Disease Investigators: Jane Turner, MS, and Amy Wohl, PhD, Los Angeles County Department of Health Services, California; David Cohn, MD, Arthur Davidson, MD, and Cornelius Rietmeijer, MD, Denver Department of Health and Hospitals, Colorado; Julia Gable, MS, and Melanie Thompson, MD, AIDS Research Consortium of Atlanta, Georgia; Stephanie Broyles, MS, and Anne Morse, BS, Louisiana Department of Health, New Orleans; Eve Mokotoff, MPH, and Linda Wotring, PhD, Michigan Department of Community Health, Detroit; Judy Sackoff, PhD, New York City Department of Health, New York; Maria de los Angeles Gomez, PhD, Robert Hunter, MD, and Jose Otero, MPH, University Central del Caribe, Bayamon, and Sandra Miranda, Puerto Rico Department of Health, San Juan; Sharon Melville, MD, and Sylvia Odem, MPH, Texas Department of Health, Austin, and Philip Keiser MD, Parkland Hospital, Dallas, Texas; Wes McNeely, MS, and Kaye Reynolds, MPH, Department of Health and Human Services, Houston, Texas; Susan Buskin, PhD, and Sharon Hopkins, DVM, Seattle-King County Department of Public Health, Washington.