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Prevalence of Clinical Symptoms Associated with Highly Active Antiretroviral Therapy in the Women's Interagency HIV Study

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Abstract

Background—The extended use of antiretroviral drugs among human immunodeficiency virus (HIV)–seropositive individuals underscores the need for a comprehensive evaluation of therapy-associated clinical symptoms.

Methods—Beginning in April 2000, 364 HIV-seronegative and 1256 HIV-seropositive women enrolled in a multicenter cohort study reported clinical symptoms that included abdominal pain, diarrhea, anorexia, nausea and/or vomiting, myalgias, fatigue, fever, body fat redistribution, dizziness, headaches, paresthesias, xerostomia, nephrolithiasis, and rash. We examined the prevalence of symptoms with respect to HIV infection and the use of highly active antiretroviral therapy (HAART), using data-correlation models.

Results—In the 6 months before a study visit, 49% of HIV-seronegative women, 67% of HIV-seropositive women not receiving therapy, and 69% of HIV-seropositive women receiving HAART reported any clinical symptom. The odds ratios (ORs) for reporting any symptom were 1.4 (95% confidence interval [CI], 1.1–1.8) for women who changed HAART regimens and 0.9 (95% CI, 0.7–1.1) for women reporting stable HAART use, compared with those reporting no therapy use. Significant findings ($P < .05$) for particular symptoms were an increased odds of diarrhea, nausea and/or vomiting, body fat redistribution, myalgias, and paresthesias, when data for women who changed HAART regimens were compared with those for women not receiving therapy. The OR for reporting any symptom was 1.5 (95% CI, 1.2–1.9) for women who switched HAART regimens and 1.6 (95% CI, 1.3–1.9) for women who discontinued HAART, compared with those reporting stable HAART use.

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Conclusions—Our findings confirm the high prevalence of clinical symptoms among HIV-seropositive women who changed HAART regimens. The high prevalence of symptoms among HIV-seronegative women and HIV-seropositive women not receiving therapy demonstrates that caution should be used when attributing the occurrence of symptoms entirely to HAART.

The effects of HAART on morbidity and mortality in HIV-infected populations are well recognized [1–3]. Current understanding of latent virus reservoirs [4] suggests that therapy may need to occur over extended periods or may be lifelong. As a consequence, recently published guidelines [5] for antiretroviral treatment (ART) of HIV infection have emphasized the balance between the potency and toxicity of ART, to guide the timing of initiation of therapy and choice of regimens.

Few studies have evaluated the association of HAART with clinical symptoms, particularly in relation to the pattern of ART use. Recent clinical trials have identified clinical symptoms associated with ART [6–10] and have found that the most common are gastrointestinal symptoms, peripheral neuropathy, rash, fatigue, and myalgias. Although clinical trials may provide more-detailed information regarding clinical symptoms than do observational studies, and although they are less prone to selection biases and residual confounding, they tend to be of shorter duration, have smaller sample sizes, and enroll selected participants [11]; thus, rates of occurrence of symptoms may not accurately reflect rates observed in clinical practice.

Cohort studies are well positioned to assess both the population impact and the effectiveness of therapies [12, 13], as well as the occurrence of clinical symptoms associated with prolonged ART use. Self-reporting of symptoms is easily ascertained from epidemiological studies of HIV-seropositive individuals and provide a mechanism to ascertain unbiased estimates of therapy-associated clinical symptoms. To date, several epidemiological studies have reported high rates of occurrence of clinical symptoms among HIV-seropositive individuals receiving ART [14–17]. However, to gain a more comprehensive understanding of the complex relationship between HIV infection and therapy-associated symptoms, we compared the occurrence of self-reported clinical symptoms among women receiving HAART with the occurrence of symptoms among HIV-seronegative women with similar demographic data and among HIV-seropositive women not receiving ART.

METHODS

Data collection and study population

The Women's Interagency HIV Study (WIHS) is a multicenter prospective cohort study consisting of 569 HIV-seronegative and 2059 HIV-seropositive women who return for follow-up every 6 months. A detailed description of the WIHS was published previously [18]. In brief, between October 1994 and November 1995, women were enrolled at 6 sites in the United States: the Bronx/Manhattan and Brooklyn, New York; Chicago; Los Angeles; San Francisco; and Washington, D.C. WIHS participants return semiannually for a physical examination, collection of specimens, and a series of interviewer-administered questionnaires obtaining information that includes the participant's use of antiretroviral medication. Plasma virus loads are measured by using isothermal nucleic acid sequence–based amplification (NASBA/Nuclisens, Organon Teknika), with a lower limit of detection of 80 copies/mL. T cell subsets are determined by using standard flow cytometry techniques [19]. For all analyses, we used $CD4^+$ cell counts instead of percentage of $CD4^+$ cells; the primary results of this study were unaffected by this choice (data not shown). $CD4^+$ cell counts and plasma virus loads were determined from stored specimens obtained at regular WIHS visits.

Beginning in April 2000, all women were administered a questionnaire at each study visit, to identify clinical symptoms experienced since their last study visit. The study population for this analysis consisted of women who completed the symptom questionnaire and who returned for consecutive study visits that were no more than 1 year apart between October 1999 (i.e., 1 study visit before the introduction of the clinical symptoms questionnaire) and April 2003. The unit of analysis was a single pair of visits, and results from up to 6 pairs of visits could be included for each participant. Symptoms included on the questionnaire were categorized as follows: (1) gastrointestinal: abdominal pain or cramps, diarrhea, lack of appetite or anorexia, and nausea and/or vomiting; (2) metabolic: fever and shifting of body fat or body fat redistribution; (3) general malaise: muscle aches/pains or myalgias and drowsiness/tiredness or fatigue; (4) neurologic: dizziness or lack of concentration, headaches, and pain/tingling in feet/hands or paresthesias; and (5) other: dry mouth or xerostomia, rash, and kidney stones or nephrolithiasis. The presence of each symptom was based on the participants' interpretation of the listed symptoms, and the participants were asked to classify severity of symptoms as "not bad," "bad," "very bad," or "terrible." For the current analysis, all symptoms were dichotomized as present (i.e., "bad," "very bad," or "terrible") or absent (i.e., not reported or "not bad"). In addition, women were classified according to whether they reported ≥1 symptom since their last study visit. Despite the subjective nature of some symptoms (particularly body fat redistribution), quality-assurance procedures to ensure standardization of data across WIHS visits and study centers have been implemented and have been described elsewhere [18]. The WIHS recently implemented a visual assessment of body fat redistribution, defined as an excess or deficit of fat at different body parts; however, this analysis relies exclusively on self-reported symptoms. Thus, the possibility remains that, with respect to therapy use, differential recall of body fat redistribution and other symptoms may have occurred.

The pattern of ART use among the HIV-seropositive women was determined for all pairs of visits, with visit dates designated as t_0 (i.e., the earlier visit of the pair) and t_1 (i.e., the later visit of the pair). ART use was categorized as follows: (1) no therapy use (i.e., reporting no ART use between t_0 and t_1) and no history of HAART; (2) stable HAART use (i.e., reporting the same HAART regimen between t_0 and t_1); (3) switching HAART use (i.e., reporting a different HAART regimen between t_0 and t_1); (4) discontinuing all HAART medications (i.e., reporting a transition from HAART use to no therapy use between t_0 and t_1) or no therapy use but with a history of HAART use; and (5) discontinuing a component of HAART (i.e., reporting a transition from HAART use to either monotherapy or a 2-drug regimen between t_0 and t_1). The use of suboptimal regimens, such as monotherapy or 2-drug regimens, was reported at a low frequency (<10%) in the WIHS and may reflect some level of nonadherence to prescribed regimens; these observations were excluded from the analysis.

In accordance with the Department of Health and Human Services/Kaiser Panel guidelines [20], HAART was defined as follows: (1) ≥2 nucleoside reverse-transcriptase inhibitors (NRTIs) in combination with at least 1 protease inhibitor (PI) or 1 nonnucleoside reverse-transcriptase inhibitor (NNRTI); (2) 1 NRTI in combination with at ≥1 PI and ≥1 NNRTI; (3) a regimen including ritonavir and saquinavir in combination with 1 NRTI and no NNRTIs; or (4) an abacavir- or tenofovir-containing regimen of ≥3 NRTIs and no PIs or NNRTIs. Combinations of zidovudine and stavudine with either a PI or an NNRTI were not considered HAART. The patterns and predictors of therapy use and switching have been described elsewhere [21, 22].

Statistical analysis

We first compared the prevalence of self-reported symptoms among HIV-seropositive women with that in a reference group of HIV-seronegative women. Second, we restricted

our analysis to data for HIV-seropositive women and compared the prevalence of self-reported symptoms among women reporting stable HAART use and women reporting any change in their HAART regimen (i.e., switching the HAART regimen, discontinuing all medications, or discontinuing a component of HAART) with that in a reference group of HIV-seropositive women reporting no therapy use. Finally, we restricted our analysis to HIV-seropositive women receiving HAART, and compared the odds of self-reported symptoms among those who switched HAART regimens or discontinued HAART (i.e., discontinued all medications or a component of HAART) with the odds of symptoms in a reference group of women reporting stable HAART use. Separate logistic regression models were constructed to evaluate the factors associated with the prevalence of each symptom. Generalized estimating equations were used [23], by means of the Proc Genmod procedure in SAS, version 8.0 (SAS Institute), to account for within-individual correlations between repeated observations. All models were adjusted for the following variables assessed at visit t_0, which were collected as part of the WIHS and which we felt might act as confounding variables: age (continuous), race/ethnicity (African American, Hispanic, white, or other), body mass index (continuous), alcohol intake since the last visit (drinks per week), and category of reported HIV risk at baseline (injection drug use, heterosexual contact, blood transfusion, or none identified). Models comparing data for HIV-seropositive women only were further adjusted for $CD4^+$ cell count (continuous), HIV RNA level (continuous), and prior report of clinical AIDS, also assessed at visit t_0.

RESULTS

Of the 2628 women enrolled in the WIHS, 849 were excluded before the administration of the symptom questionnaire, and 159 did not return for consecutive study visits, resulting in a final study population of 364 HIV-seronegative and 1256 HIV-seropositive women. The women included were slightly younger, had less-advanced HIV disease at baseline, and were more likely to be of nonwhite ethnicity, compared with those who were excluded (data not shown). Averages of 4.8 and 4.7 observations per woman were included for HIV-seronegative and HIV-seropositive women, respectively. Differences in descriptive data for HIV-seronegative and HIV-seropositive women are displayed in table 1.

The prevalence of each self-reported symptom is listed in table 2, by HIV status and category of ART use. The highest prevalences for individual symptoms were observed among those who discontinued all medications (highest prevalence for 7 of 14 symptoms) and those who switched HAART regimens (highest prevalence for 5 of 14 symptoms). Fatigue was the most common clinical symptom, followed by headaches and myalgias. Additional analyses of the occurrence of nephrolithiasis are not presented, because of the low prevalence of this symptom. The most commonly reported categories of symptoms were general malaise and neurologic symptoms. Finally, we observed a high prevalence of ≥1 symptom for each category of HIV status or ART use, which ranged from 48.6% among HIV-seronegative women to 74.9% among those who switched HAART regimens.

HIV-seropositive women had a statistically significantly higher odds ($P < .05$) of reporting each of the symptoms, compared with HIV-seronegative women (figure 1). The highest ORs were found for body fat redistribution (4.9; 95% CI, 3.4–7.0) and diarrhea (3.3; 95% CI, 2.3–5.0). Overall, the odds of HIV-seropositive women reporting ≥1 symptom were 2.2 times higher (95% CI, 1.8–2.6) than that for HIV-seronegative women.

Among women who changed therapy regimens, symptoms that demonstrated a clear therapy-associated effect (i.e., higher odds among HIV-seropositive women receiving HAART than among HIV-seropositive women not receiving ART) were diarrhea, nausea and/or vomiting, body fat redistribution, myalgias, and paresthesias (figure 2). For women

receiving stable HAART regimens, the odds of reporting body fat redistribution were 3.2 times higher (95% CI, 2.2–4.6) than that for women not receiving ART. Women receiving stable regimens had a statistically significantly lower odds ($P < .05$) of reporting abdominal pain or cramps and a statistically significantly higher odds ($P < .05$) of reporting diarrhea and body fat redistribution, compared with those reporting no ART use. Overall, the odds of reporting ≥1 symptom were 1.4 times higher (95% CI, 1.1–1.8) for women who changed HAART regimens and 0.9 times lower (95% CI, 0.7–1.1) for those receiving stable HAART regimens, compared with those reporting no ART use.

Compared with women reporting stable HAART use, the odds of reporting diarrhea, anorexia, nausea and/or vomiting, fever, body fat redistribution, dizziness, xerostomia, or rash were statistically significantly higher ($P < .05$) for women who switched HAART regimens (figure 3). The odds of the occurrence of any self-reported symptom, except diarrhea and body fat redistribution, were higher for those who discontinued HAART, compared with those reporting stable HAART use. Overall, the odds of reporting ≥1 symptom were 1.5 times higher (95% CI, 1.2–1.9) for women who switched HAART regimens and 1.6 times higher (95% CI, 1.3–1.9) for those who discontinued HAART, compared with women reporting stable HAART use.

DISCUSSION

To date, this study is the largest to examine clinical symptoms in a cohort of HIV-seropositive and high-risk HIV-seronegative women. We documented the highest prevalence of symptoms during a 6-month period before a study visit among those who switched HAART regimens or discontinued all medications and the lowest prevalence among HIV-seronegative women. Significant findings included an increased prevalence of diarrhea, nausea and/or vomiting, body fat redistribution, myalgias, and paresthesias among women who changed HAART regimens, compared with those not receiving ART. An important strength of our study was the availability of appropriate control groups for comparison of the occurrence of side effects among HAART recipients. Furthermore, clinical symptoms were assessed across the entire cohort and in the same manner for all women, regardless of HIV status or category of ART use.

Previous observational studies have reported a high incidence of laboratory adverse effects or self-reported symptoms among HIV-seropositive individuals receiving treatment [14–17]. Lucas et al. [14] observed 273 patients who initiated HAART, for an average of 15 months, and reported known laboratory adverse effects or clinical symptoms in 29% of patients. Bonfanti et al. [15] observed 1207 patients who had started a PI-containing regimen and did not discontinue therapy, for an average of 11 months, and reported laboratory adverse effects or clinical symptoms in 36% of patients. In a cross-sectional study of 1160 patients receiving HAART, Fellay et al. [16] reported a prevalence of self-reported clinical symptoms of 78% during a 30-day period. Similar rates of occurrence were reported in a recent cross-sectional study [17] of 109 patients receiving HAART, with the highest prevalences observed for fatigue, aching muscles and joints, and diarrhea. In our study, 49% of HIV-seronegative women, 67% of HIV-seropositive women not receiving ART, and 69% of HIV-seropositive women receiving HAART reported at least 1 clinical symptom during the previous 6 months. The rates of occurrence that we found are most consistent with those reported in the 2 cross-sectional studies [16, 17], which ascertained clinical events retrospectively and did not exclude events that patients reported as not attributable to their medications.

The etiology of clinical symptoms among individuals infected with HIV is complex and may be associated with ART use, the stage of HIV disease, or both. We evaluated 6 groups of

women according to HIV status and category of ART use, and several interesting patterns emerged. First, all 14 symptoms had some association with the presence of HIV infection. Second, for women reporting stable HAART use, the odds for the occurrence of any of the symptoms were equivalent to that for women reporting no ART use, with the exception of a higher odds for the occurrence of diarrhea and body fat redistribution. Third, compared with women who reported no ART use, women who reported changing HAART regimens had a higher odds of reporting symptoms, including diarrhea, nausea and/or vomiting, body fat redistribution, myalgias, and paresthesias. Finally, among HIV-seropositive women receiving HAART, those with stable HAART regimens had the lowest risk for clinical symptoms, particularly when compared with those who discontinued HAART. Our study is the first to evaluate clinical symptoms among multiple control groups in the era of HAART; thus, direct comparisons with prior studies is not possible.

Body fat redistribution and diarrhea were most consistently associated with therapy use, because these were the only symptoms associated with both changing and stable HAART regimens. Furthermore, compared with stable HAART use, the odds for the reporting of body fat redistribution and diarrhea were higher for women who switched regimens but not for women who discontinued HAART. One potential explanation for these observations is that these symptoms may have been an indication for medical providers to switch HAART regimens but were not an immediate reason for discontinuing medications. Given the potential for the misclassification of body fat redistribution, these results should be confirmed by other studies specifically designed to capture lipodistrophy.

Because the clinical symptoms were assessed by self-reporting, our results may be influenced by recall bias. For example, persons who were not receiving HAART or those reporting stable HAART use may have less-accurate recall of symptoms, compared with those who switched regimens or discontinued HAART. Therefore, we repeated the analysis after defining symptoms as present only if the woman reported the symptom in the most severe category (i.e., “terrible”). If recall bias was influencing our results, we would expect an even more pronounced treatment effect when using the most severe category for analysis; however, the conclusions were unchanged (data not shown). In addition, substantial efforts were made to ensure that the collection of data was standardized for all participants and across all WIHS visits. Nevertheless, these factors do not conclusively demonstrate the absence of recall bias.

Depression may have been a confounding variable in our data, because it is related to nonspecific symptoms, such as myalgias, fatigue, and headaches, and to both HIV infection [24, 25] and HAART use [26, 27]. The reported models, however, did not adjust for depression, because the Center for Epidemiological Studies Depression Scale was not administered at every study visit. In separate analyses that adjusted for depression, the magnitude of the ORs was not affected for individual symptoms, although the decreased number of observations reduced the statistical significance (data not shown); thus, depression was not an important confounding variable in our data. An additional limitation of this study was that the symptoms and the patterns of therapy use were assessed at the same time during consecutive study visits. Thus, whether the reported side effects occurred before or after the therapy change cannot be determined conclusively. Because the discontinuation of therapy may be associated with a rebound in HIV RNA level or a decrease in $CD4^+$ cell count [28], individuals may have experienced more HIV-related symptoms after discontinuation. However, it is more likely that clinical symptoms resulted in a clinician or patient decision to modify or discontinue the therapy regimen [29, 30].

In a well-characterized cohort of high-risk HIV-seronegative and HIV-seropositive women, we documented the high prevalence of self-reported clinical symptoms. Using appropriate

control groups—namely, HIV-seronegative women, HIV-seropositive women not receiving therapy, and HIV-seropositive women receiving stable HAART regimens—we were able to identify symptoms associated with therapy use, HIV infection, or both. Although the women were aware of their HIV status and the use of therapies, the assessment of clinical symptoms across the entire cohort attempts the most unbiased comparison possible of the prevalence of clinical symptoms in an observational cohort study. Furthermore, multivariable adjustment for other factors associated with symptoms and ART use helped to ensure the comparability of groups apart from HIV status and category of therapy use.

Our findings confirm the need to closely monitor the clinical symptoms of women on ART. Of particular concern were symptoms such as diarrhea, nausea and/or vomiting, body fat redistribution, myalgias, and paresthesias; these symptoms were associated with a change in the therapy regimen, the majority of which involved the discontinuation of HAART or a component of HAART. However, our findings also reveal the need for caution in attributing clinical symptoms in HIV disease entirely to therapy use, given the high prevalence of symptoms among high-risk HIV-seronegative women and HAART-naive HIV-seropositive women.

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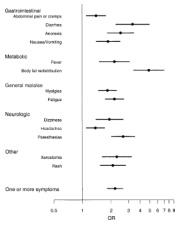

Figure 1.

Multivariable ORs and 95% CIs for clinical symptoms among participants in the Women's Interagency HIV Study. Reference group consists of HIV-seronegative women. Covariates included in the models were age, race/ethnicity, body mass index, category of HIV risk at baseline, and alcohol intake.

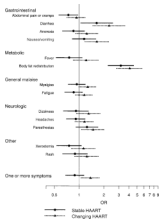

Figure 2.

Multivariable ORs and 95% CIs for clinical symptoms among HIV-seropositive women. Reference group consists of HIV-seropositive women reporting no therapy use. Covariates included in the models were age, race/ethnicity, body mass index, category of HIV risk at baseline, alcohol intake, $CD4^+$ cell count, HIV RNA level, and prior diagnosis of AIDS.

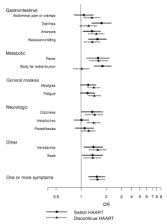

Figure 3.

Multivariable ORs and 95% CIs for clinical symptoms among HIV-seropositive women receiving HAART. Reference group consists of women reporting stable HAART use. Covariates included in the models were age, race/ethnicity, body mass index, category of HIV risk at baseline, alcohol intake, $CD4^+$ cell count, HIV RNA level, and prior diagnosis of AIDS.

Table 1

Descriptive variables for participants in the Women's Interagency HIV Study, by HIV status and category of HAART use.

Variable	HIV-seronegative women	HIV-seropositive women				
		HAART naive	Stable HAART use	Switch in HAART regimen	Discontinuation of all medication	Discontinuation of a component of HAART[a]
No. of women	364	268	908	413	507	125
No. of pairs of visits[b]	1826	1107	2856	696	1233	141
Age, median years	41.1	41.7	**42.5**	41.7	40.8	**42.7**
Race/ethnicity						
African American	60.7	**64.2**	**54.2**	**47.7**	57.1	**61.7**
Hispanic	27.0	**19.0**	**24.8**	**31.9**	29.0	**17.7**
White	9.8	**13.8**	**18.3**	**18.1**	11.0	**17.0**
Other[c]	2.6	**3.0**	**2.6**	**2.3**	2.9	**3.6**
Median body mass index	29.1	**27.6**	**26.2**	**26.3**	**26.6**	**26.2**
Category of HIV risk at baseline						
Injection drug use	25.0	**41.2**	**31.4**	**26.9**	**31.1**	**40.6**
Heterosexual contact	29.7	**33.0**	**43.1**	**47.1**	**42.5**	**35.5**
Blood transfusion	3.0	**2.5**	**4.0**	**3.6**	**4.6**	**2.2**
None identified	42.3	**23.3**	**21.5**	**22.4**	**21.8**	**21.7**
Alcohol intake						
None	50.6	53.1	**62.2**	**63.5**	**59.7**	58.7
≤1 drink/week	18.6	16.2	**16.7**	**17.1**	**15.0**	18.1
>1 drink/week	30.8	30.8	**21.1**	**19.4**	**25.3**	23.2
$CD4^+$ cell count, median cells/μL	…	473	424	320	335	325
HIV load <80 copies/mL	…	17.9	48.5	30.8	13.0	30.2
Prior diagnosis of AIDS	…	39.6	51.2	57.9	51.9	58.2

NOTE. Data are percentage of pairs of visits contributed by women, unless otherwise indicated. Boldface indicates a statistically significant difference ($P < .05$), compared with HIV-seronegative women.

[a] Transition to monotherapy or a 2-drug regimen.

[b] Corresponds to a pair of study visits ≤1 year apart for a given woman.

[c] Includes Asian, Pacific Islander, Native American, and Alaskan.

Table 2

Prevalence of clinical symptoms among participants in the Women's Interagency HIV Study, by HIV status and category of HAART use.

Category, symptom	HIV-seronegative women, %	HAART naive	Stable HAART use	Switch in HAART regimen	Discontinuation of all medication	Discontinuation of a component of HAART[a]
No. of pairs of visits	1826	1107	2856	696	1233	141
Gastrointestinal	20.4	**34.0**	**34.1**	**41.8**	**39.9**	**37.6**
Abdominal pain or cramps	12.1	**18.4**	**15.2**	**16.2**	**19.2**	16.3
Diarrhea	3.2	**6.1**	**10.0**	**17.7**	**11.6**	**11.4**
Anorexia	6.8	**15.8**	**14.6**	**19.2**	**20.7**	**19.9**
Nausea and/or vomiting	7.2	**9.6**	**11.3**	**18.1**	**15.3**	**17.0**
Metabolic	6.1	**12.4**	**19.4**	**30.3**	**21.3**	**24.8**
Fever	3.6	**8.1**	**6.3**	**10.8**	**10.5**	**9.9**
Body fat redistribution	3.0	**5.2**	**14.9**	**23.6**	**12.9**	**17.7**
General malaise	26.3	**44.4**	**41.3**	**47.0**	**50.1**	**48.2**
Myalgias	16.5	**26.7**	**26.0**	**29.7**	**32.3**	**30.5**
Fatigue	18.2	**33.0**	**31.2**	**36.4**	**38.9**	**40.4**
Neurologic	27.7	**39.0**	**40.2**	**45.1**	**49.6**	**47.5**
Dizziness or lack of concentration	6.4	**11.3**	**11.1**	**14.9**	**16.0**	**12.8**
Headaches	21.8	**29.1**	**26.2**	**28.0**	**35.4**	**29.1**
Paresthesias	9.2	**17.1**	**21.3**	**23.0**	**24.7**	**22.7**
Other	11.0	**22.3**	**19.3**	**27.0**	**28.1**	**20.6**
Xerostomia	6.9	**16.2**	**13.1**	**18.4**	**18.7**	**16.3**
Rash	5.0	**8.7**	**8.4**	**13.7**	**13.6**	7.9
Nephrolithiasis	0.8	1.5	1.0	1.3	1.0	1.4
≥1 Symptom	48.6	**66.8**	**65.1**	**74.9**	**74.1**	**70.2**

NOTE. Data are percentage of pairs of visits contributed by women, unless otherwise indicated. Boldface indicates a statistically significant difference ($P < .05$), compared with HIV-seronegative women.

[a] Transition to monotherapy or a 2-drug regimen.