

Healthcare use by varied highly active antiretroviral therapy (HAART) strata: HAART use, discontinuation, and naivety

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Objectives: Prior reports have found a temporal association between the introduction of highly active antiretroviral therapy (HAART) and population rates of health service use among persons living with HIV. Our objective was to explore further the effect of HAART by comparing healthcare use among persons who use HAART and persons who discontinue HAART to that among HAART-naive and HIV-negative persons.

Methods: Longitudinal analyses of 1485 women with and at-risk for HIV who contributed data to the Women's Interagency HIV Study between April 1997 and March 2000.

Results: Compared with HAART-naive women, those using HAART had a higher probability of more than three primary care visits per 6 months [odds ratio (OR), 1.38; 95% confidence interval (CI), 1.16–1.65], a lower probability of more than one emergency room visit per 6 months (OR, 0.75; CI, 0.59–0.95), and a lower probability of more than one hospitalization per 6 months (OR, 0.67; CI, 0.51–0.88). Compared with HAART-naive women, women who had discontinued HAART had a higher frequency of primary care visits (OR, 1.57; CI, 1.26–1.97) but did not demonstrate a significant change in emergency room or hospital use. Modeling of a standardized population HIV-positive women without AIDS indicated hospitalization and emergency room use among HAART users was equivalent to that among HIV-negative women.

Conclusions: HIV-positive HAART users (without AIDS) exhibited emergency room and hospitalization use patterns equivalent to those of HIV-negative women. Furthermore, the discontinuation of HAART was associated with a loss of the reduction in hospital use that was achieved with HAART.

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Introduction

As more experience with highly active antiretroviral therapy (HAART) regimens for the treatment of HIV

has been gained over the past several years, there is increased recognition of the diversity of potentially serious adverse clinical events associated with these treatments. Potential adverse effects include hepatotoxi-

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city [1,2], impaired glucose metabolism and diabetes mellitus [3–6], hyperlactatemia [7–9], hyperlipidemia [3–6,10] and fat redistribution [3,6,8].

Most of the previous reports that have examined the effects of HAART on the frequency and/or cost of healthcare service use have taken an ecological approach to the analyses (e.g., explored associations between population prevalence of HAART use and population hospitalization rates and/or costs) [11–20]. A few reports compared healthcare service use and/or costs among persons on HAART to those not on HAART [20–23]. While the slowing of disease progression might be expected to be associated with decreased health service use, clinical monitoring requirements for effective HAART therapy and the potentially accumulating need for management of HAART side effects might be expected to be associated with increased service use. In this report we examine the effect of HAART on healthcare utilization from 1997 through 2000. We used two analytic approaches: an individual approach and a complementary population-based approach.

Methods

Study population and design overview

The Women's Interagency HIV Study (WIHS) is a multi-site cohort study of women with and at risk for HIV infection in the USA. Between October 1994 and November 1995 we enrolled 2628 women (2059 HIV-positive women and 569 HIV-negative women) at six sites: Bronx/Manhattan, New York; Brooklyn, New York; Chicago, Illinois; Los Angeles, California; Northern California; and Washington, D.C. Participants undergo follow-up study visits at 6-month intervals. At each study visit we perform detailed interviews, physical examination, and laboratory specimen collection. A description of WIHS enrollment and study design have been presented elsewhere [24]. The Institutional Review Boards of all participating sites approved the study, and informed consent was obtained from all participants prior to enrollment.

We aimed to quantify the individual effectiveness of HAART [25] on healthcare service use. For this report we used the longitudinal interview and laboratory data to assess associations between HAART use and HAART discontinuation on healthcare service use. Our eligible study population consisted of women who contributed data on healthcare use between April 1997 and March 2000 [26,27]. We excluded 240 women who reported a pregnancy at any point during the analysis period to eliminate the high frequency of healthcare use associated solely with prenatal care. We also excluded nine women who seroconverted during

the study period to simplify the analyses to women with stable serostatus.

Data collection

Our analyses included self-reported interview data collected at each study visit, such as demographic information (age, race/ethnicity, employment status, and health insurance status), medical history (diagnoses of AIDS-defining clinical conditions [28,29]), medication use, and healthcare utilization. To enhance participant recall regarding medications, interviewers showed participants pictures of antiretroviral medications and referred to the medications by trade name, generic name and chemical name. Healthcare utilization data included frequencies of primary care visits, emergency room visits, and hospitalizations since the previous study visit. We used the following laboratory data for our analyses: HIV-antibody testing by enzyme-linked immunoabsorbant serum assay plus confirmatory Western blot (baseline for all participants and at each follow-up visit for HIV-negative participants); CD4 cell count; and HIV ribonucleic acid (HIV RNA) quantification by nucleic acid sequence based (NASBA/Nuclisens) method (Organon Teknica, Durham, North Carolina, USA) for all HIV-positive participants.

Predictor variables

Our main predictor variable was HAART use. We used self-reported data on antiretroviral medication use to construct the HAART use variable according to published treatment guidelines issued by the United States Department of Health and Human Services [30–33] and the International AIDS Society-USA [34–36] during the study period. In order to capture the broad range of regimens in use during the study period we constructed our HAART variable to include regimens listed as 'recommended' or 'under evaluation' in the year 2000 treatment guidelines [33,36]. Specifically, we defined HAART as: two or more nucleoside reverse transcriptase inhibitors (NRTI) plus one or two protease inhibitors (PI); two or more NRTI plus one non-nucleoside reverse transcriptase inhibitor (NNRTI); one NRTI with at least one PI and one NNRTI; three NRTI if one of them was abacavir. Regimens in which the two NRTI consisted of zidovudine plus stavudine were not considered HAART. At each WIHS study visit we characterized participants as either: never having received HAART ('HAART-naive'); having received HAART during the 12–6-month interval prior to the visit ('HAART'); or not having received HAART during the 12–6-month interval prior to the study visit, but having used HAART prior to that interval ('HAART-discontinued').

Outcome variables

We examined three healthcare utilization outcomes: primary care visits, emergency room visits and hospita-

lizations. Primary care visits were defined as outpatient visits with the provider that the participant consulted for over 50% of their medical care (excluding providers in an emergency room or jail). Because the distribution of the number of healthcare visits was highly skewed (few had a large number of visits), and because the distribution had an unduly preponderance of zeros (making standard Poisson methods unsuitable), we elected to simplify the analysis by dichotomizing the outcome measures as follows: ≤ 3 versus > 3 primary care visits; ≤ 1 versus > 1 emergency room visits; and ≤ 1 versus > 1 hospitalization, all scaled to represent the number of healthcare visits per 6-month interval.

Statistical analyses

Using person-visits as the units of analyses, we performed multivariate logistic regression analyses to identify the effect of HAART use on subsequent healthcare utilization. For the HIV-positive women, we used six indicator variables to describe HAART use status (as described under Predictor Variables) and clinical status [without an AIDS clinical diagnosis ('HIV+') versus with an AIDS clinical diagnosis ('AIDS')] as follows: HIV+, HAART-naive; HIV+, HAART; HIV+, HAART-discontinued; AIDS, HAART-naive; AIDS, HAART; AIDS, HAART-discontinued. HIV-negative women served as the reference category. To adjust for the correlation of repeated measurements encountered in the longitudinal data, we derived estimates and 95% confidence intervals (CI) for each subgroup using the SAS GENMOD procedure with generalized estimating equations (SAS Institute, Cary, North Carolina, USA).

Since both CD4 cell count and HIV RNA help determine when HAART is initiated, we adjusted for them as confounding variables in our analyses. We transformed CD4 cell counts and HIV RNA measurements so we could make meaningful comparisons of healthcare utilization across our subgroups. Specifically, for HIV+ women without AIDS we rescaled the CD4 cell count variable as $(CD4-350)/100$ and the HIV RNA variable as $\log_{10}(HIV\ RNA/10\ 000)$; for those women with AIDS we rescaled CD4 cell count as $(CD4-150)/100$ and HIV RNA as $\log_{10}(HIV\ RNA/50\ 000)$. For HIV-negative women (for whom CD4 cell count and HIV RNA are irrelevant) we did not include their effect in the model. The limits of detection for HIV RNA improved during the study period, therefore we used the highest level of detection (4000 copies/ml) to standardize HIV RNA measurements. To examine the effect of HAART on health care service use by selected demographic characteristics we stratified the study population by race/ethnicity, insurance and employment status.

Among HAART users we assessed only healthcare utilization that occurred after HAART initiation was reported to ascribe to the epidemiologic principle of

exposure (HAART use) preceding the outcome of interest (frequency of healthcare visits). Furthermore, we assessed healthcare utilization that occurred at least 1 year after HAART initiation to exclude measurements of transient increases in healthcare utilization frequently associated with HAART initiation. Since CD4 cell count and HIV RNA are both directly affected as a result of HAART, it would have been inappropriate to update the time-dependent covariates after HAART initiation. Rather, we used the measures obtained at the last 'pre-HAART' WIHS study visit, i.e., the study visit that preceded the one at which HAART initiation was reported. In summary, each record for the analysis was based on data collected at three consecutive WIHS study visits. Specifically, laboratory markers were taken from study visit one of three for HAART-naive individuals and from the last pre-HAART visit for HAART-experienced individuals, HAART use was based on study visit two of three, and healthcare service use was based on study visit three of three.

We also performed an analysis using a population-based approach to assess the robustness of our main findings. Specifically, we evaluated the overall proportion of participants reporting each of the three health service use outcomes over time. The study period for this analysis (October 1995–March 2000) was divided into four calendar periods based on the proportion of respondents reporting having ever used HAART: low HAART-use era during which only 4% of the study cohort used HAART (October 1995–September 1996); moderate HAART-use era during which the prevalence of HAART use increased to 17% (October 1996–March 1997); early high HAART-use era during which HAART became the most common regimen at 59% (April 1997–September 1998); and established high HAART-use era during which 74% of the study cohort reported HAART use (October 1998–March 2000).

Results

Demographics

Out of 2628 total women who enrolled in the WIHS, there were 2001 (76%) seen during the period for this analysis—April 1997 to March 2000. Of these, we excluded 240 (21%) women who became pregnant and nine women who seroconverted during the study period. We excluded an additional 267 women due to missing data for key variables. Thus we analyzed data for 1485 women (57% of the original cohort) who contributed a total of 5603 person-visits (i.e., study participants' contribution of semi-annual WIHS study visits).

Table 1 presents a summary of demographic characteristics of our study population using person-visits as the unit of analysis. African-Americans and Latinas comprised over 75% of our study population across all subgroups, reflective of the epidemiology of HIV/AIDS among women in the USA [37]. The median age ranged from 39.8 to 41.8 years. Employment rates were low overall, ranging from 17.7% to 43.6%.

Within a particular disease-stage subgroup the distribution of demographic characteristics varied by HAART status (Table 1). For example, within the HIV+ group (i.e., without AIDS), those who were HAART-naive were more likely to be African-American (61.9%) than were either HAART users (46.0%; $P < 0.001$) or HAART discontinuers (45.1%; $P = 0.002$). Also within the HIV+ group, HAART-naive women were less likely to be Latina (20.7%) than were HAART users (30.6%; $P = 0.007$) or HAART discontinuers (39.0%; $P < 0.001$). These differences in racial/ethnic distribution by HAART-use category were not as pronounced among women with AIDS (Table 1). Overall insurance rates did not vary by HAART-use category (Table 1), though the specific type of insurance did. For example, among women without AIDS, HAART users were more likely to have private insurance (33.2%) than

were either HAART-naive women (24.3%; $P = 0.028$) or HAART-discontinuers (23.3%; $P = 0.034$). Among women with AIDS, HAART users were more likely to have private insurance (18.6%) than HAART-naive women (8.9%; $P = 0.004$). Furthermore, HAART users were more likely to have other types of insurance (19.4%) than were HAART-naive women (10.6%; $P = 0.004$) or HAART discontinuers (10.3%; $P = 0.014$). Within both the HIV+ and the AIDS groups, employment levels were higher among HAART users compared with women in other HAART-use categories (Table 1). HIV-negative women were the most likely of all groups to be employed (43.6%), but the least likely to be insured (39.3%). The distribution of race/ethnicity among HIV-negative women was similar to that among HAART-naive women with and without AIDS (Table 1).

Distribution of healthcare visits

Overall, the proportion of women reporting over three primary care visits per 6 months was 42%, with a range of 21.0% among HIV-negative women to 66.1% among women with AIDS who had discontinued HAART (Table 2).

Table 1. Characteristics of the study population, Women's Interagency HIV Study, April 1997 to March 2000.

	HIV-	HIV+/non-AIDS HAART-naive	HIV+/non-AIDS HAART	HIV+/non-AIDS HAART-discontinued	HIV+/AIDS HAART-naive	HIV+/AIDS HAART	HIV+/AIDS HAART-discontinued
Person-visits (n)	1383	1269	779	264	938	709	261
Ethnicity (n = 1377)	(n = 1266)	(n = 779)	(n = 264)	(n = 937)	(n = 709)	(n = 261)	
African-American	60.1%	61.9%	46.0%	45.1%	62.4%	48.8%	52.1%
Latina	23.8%	20.7%	30.6%	39.0%	20.4%	26.7%	33.7%
White	13.7%	14.7%	20.8%	12.5%	15.4%	21.2%	11.1%
Other	2.3%	2.8%	2.7%	3.4%	1.8%	3.4%	3.1%
Age (years) (n = 1383)	(n = 1269)	(n = 779)	(n = 264)	(n = 938)	(n = 709)	(n = 261)	
Mean	40.7	39.8	41.2	40.3	41.8	41.3	41.4
Health insurance status ^a (n = 1364)	(n = 1264)	(n = 770)	(n = 260)	(n = 928)	(n = 704)	(n = 258)	
Uninsured	39.3%	19.0%	16.6%	16.5%	15.8%	13.5%	13.2%
Insured	60.7%	81.0%	83.4%	83.5%	84.2%	86.5%	86.8%
Medicaid ^b	59.1%	70.3%	62.3%	69.8%	81.2%	72.9%	80.0%
Medicare ^b	5.8%	6.1%	9.9%	9.6%	11.7%	18.7%	18.8%
Private ^b	27.3%	24.3%	33.2%	23.3%	8.9%	18.6%	14.8%
Other ^b	27.6%	17.9%	26.1%	21.9%	10.6%	19.4%	10.3%
Employment status ^a (n = 1378)	(n = 1265)	(n = 779)	(n = 264)	(n = 935)	(n = 706)	(n = 261)	
Employed	43.6%	30.7%	38.3%	32.6%	17.7%	25.2%	18.8%
Annual household income ^a (n = 1341)	(n = 1245)	(n = 765)	(n = 262)	(n = 917)	(n = 691)	(n = 258)	
≤ \$12 000 (%)	57.2	58.2	47.7	61.5	68.6	57.6	55.4%
HIV markers							
CD4 cell count (× 10 ⁶ /l) (n = 1383)	(n = 1269)	(n = 779)	(n = 264)	(n = 938)	(n = 709)	(n = 261)	
Median	1016	447	312	373	358	228	205
Interquartile range	804-1271	310-600	211-458	193-489	200-574	102-355	88-398
HIV RNA (copies/ml) (n = 1383)	(n = 1269)	(n = 779)	(n = 264)	(n = 938)	(n = 970)	(n = 970)	
% ≤ 4000 (%)	NA	60.3%	40.3%	30.3%	47.3%	29.1%	22.6%
If > 4000	NA	(n = 504)	(n = 465)	(n = 184)	(n = 495)	(n = 503)	(n = 202)
Median	NA	20 000	27 000	27 000	35 000	46 000	59 500
Interquartile range	NA	8750-50 500	11 000-66 000	7750-59 000	13 000-100 000	15 000-150 000	23 000-190 000

^aHealth insurance status, employment status, and annual household income were assessed at one visit (approximately 6 months) prior to the visit at which healthcare services were measured. ^bCategories of insurance types (among insured women) are not mutually exclusive. HAART, Highly active antiretroviral therapy; NA, not applicable.

Table 2. Healthcare service use in the Women's Interagency HIV Study from April 1997 to March 2000.

	HIV–	HIV+/non-AIDS HAART-naive	HIV+/non-AIDS HAART	HIV+/non-AIDS HAART-discontinued	HIV+/AIDS HAART-naive	HIV+/AIDS HAART	HIV+/AIDS HAART-discontinued	Overall
Number of Person-visits	1383	1269	779	264	938	709	261	5603
Primary care provider visits/6 months (%)	(n = 1379)	(n = 1266)	(n = 778)	(n = 263)	(n = 930)	(n = 707)	(n = 260)	(n = 5583)
0	50.3	24.6	10.5	13.7	18.9	9.1	10.8	24.9
1–3	28.7	39.7	36.5	31.2	32.5	31.7	23.1	33.1
> 3	21.0	35.7	53.0	55.1	48.6	59.2	66.1	42.0
Emergency room visits/6 months (%)	(n = 1380)	(n = 1265)	(n = 779)	(n = 264)	(n = 934)	(n = 708)	(n = 260)	(n = 5590)
0	85.3	84.0	85.5	86.0	72.0	79.5	74.2	81.6
1	5.4	5.8	6.2	4.9	9.3	4.9	8.5	6.3
> 1	9.4	10.2	8.3	9.1	18.7	15.6	17.3	12.1
Hospitalizations/6 months (%)	(n = 1381)	(n = 1266)	(n = 777)	(n = 264)	(n = 936)	(n = 709)	(n = 261)	(n = 5594)
0	90.4	88.4	88.2	86.0	75.5	79.7	73.6	84.8
1	4.6	4.5	6.2	4.9	8.9	8.6	8.8	6.2
> 1	5.0	7.1	5.7	9.1	15.6	11.7	17.6	9.0

HAART, Highly active antiretroviral therapy.

Overall, 12.1% of the cohort reported having over one emergency room visits per 6 months, with a range of 8.3% among HIV+ HAART users to 18.7% among women with AIDS who were HAART-naive (Table 2). Nine percent of our study population reported over one hospitalization per 6 months, with a range from 5.0% among HIV-negative women to 17.6% among women with AIDS who had discontinued HAART (Table 2).

Association between HAART use and healthcare utilization: results of individual analytic approach

The results of logistic regression analyses modeling the effect of HAART on healthcare service use are represented in Table 3. As the 95% CI for the odds ratios (OR) obtained for the HIV+ group (non-AIDS) overlapped substantially with the corresponding 95% CI for the AIDS group, we pooled the effects of HAART for the HIV+ and the AIDS groups to arrive at a summary measure (Table 3). Compared with HAART naivety, both HAART use (OR, 1.38; 95% CI, 1.16–1.65) and HAART discontinuation (OR, 1.57; 95% CI, 1.26–1.97) were associated with a higher probability of more than three primary care visits per 6 months. In contrast, HAART use was associated with a lower probability of more than one emergency room visit (OR, 0.75; 95% CI, 0.59–0.95) and a lower probability of more than one hospitalization per 6 months (OR, 0.67; 95% CI, 0.51–0.88), compared with HAART naivety. We did not observe a statistically significant reduction in either emergency room use or hospitalization among women who had discontinued HAART.

To depict graphically the influence of HAART on healthcare use based on our data, in Fig. 1 we standar-

dized the population of HIV+ women to a CD4 cell count of $350 \times 10^6/l$ and an HIV RNA load of 10 000 copies/ml, and standardized the population of women with AIDS to a CD4 cell count of $150 \times 10^6/l$ and an HIV RNA load of 50 000 copies/ml (with HIV-negative women as the reference group). The graphical presentation of this logistic regression model illustrates three main findings. First, within the HIV+ group (without AIDS), HAART use is associated with very low levels of predicted emergency room use and hospital use—equivalent to levels of service use predicted among HIV-negative women (Fig. 1). Second, discontinued HAART within this group is associated only with lower emergency room use (the probability of more than one hospitalization was similar to that predicted among HAART-naive women). Third, within the AIDS group, levels of utilization of all three health services remain well elevated above those predicted for the reference group (HIV-negative women) regardless of HAART use category.

In Table 4 we present results of analyses stratified by key potential confounders as follows: four insurance/employment strata (unemployed uninsured, unemployed insured, employed uninsured, employed insured) and three race/ethnicity strata (African-American, Latina, white). Within all subgroups HAART use was associated with a higher probability of frequent primary care visits (Table 4). Within the insurance/employment strata the magnitude of association between HAART use and primary care visits was strongest among the unemployed uninsured women (OR, 2.95; 95% CI, 1.79–4.48), followed by the employed insured (OR, 1.67; 95% CI, 1.18–2.36), and the unemployed insured (OR, 1.30; 95% CI, 1.04–1.62). Within the race/ethnicity strata the magnitude of association was similar for the Latina subgroup (OR,

Table 3. Adjusted^a odds ratios (95% confidence intervals) of healthcare service utilization for highly active antiretroviral therapy (HAART)^b or HAART-discontinued subjects versus HAART-naive subjects according to AIDS Status^c.

Healthcare service utilization	Non-AIDS		AIDS		Non-AIDS or AIDS ^b	
	HAART versus HAART-naive	HAART-discontinued versus HAART-naive	HAART versus HAART-naive	HAART-discontinued versus HAART-naive	HAART versus HAART-naive	HAART-discontinued versus HAART-naive
> 3 visits to primary care provider/6 months	1.53 (1.21–1.92)	1.68 (1.23–2.29)	1.22 (0.95–1.58)	1.46 (1.08–1.97)	1.38 (1.16–1.65)	1.57 (1.26–1.97)
> 1 visit to emergency room/6 months	0.79 (0.56–1.12)	0.80 (0.48–1.33)	0.72 (0.52–0.99)	0.78 (0.52–1.16)	0.75 (0.59–0.95)	0.79 (0.57–1.08)
> 1 hospitalization/6 months	0.72 (0.49–1.07)	1.10 (0.67–1.81)	0.64 (0.45–0.92)	0.94 (0.62–1.42)	0.67 (0.51–0.88)	0.99(0.72–1.38)

^aAdjusted by CD4 cell count and HIV RNA level. ^bOdds Ratios were obtained from a multiple logistic regression model in which we assumed that the effect of HAART for the non-AIDS and AIDS groups were the same. ^cNumbers in bold type are significant at $\alpha = 0.05$.

1.43; 95% CI, 1.02–2.02) and the African-American subgroup (OR, 1.43; 95% CI, 1.12–1.81). We observed a similar pattern among women who discontinued HAART (Table 4).

Stratification by insurance/employment status and race/ethnicity yielded a more complex picture of the associations between HAART use and either emergency room use or hospitalizations. Among unemployed insured women, HAART users (OR, 0.76; 95% CI, 0.57–1.00) and HAART discontinuers (OR, 0.66; 95% CI, 0.45–0.97) were less likely to have more than one emergency room visit per 6 months than were HAART-naive women. With respect to hospitalizations, HAART use was associated with a lower probability of more than one hospitalization among unemployed insured women (OR, 0.66; 95% CI, 0.48–0.90). In contrast, discontinued HAART was associated with a higher probability of more than one hospitalization among employed insured women (OR, 2.96; 95% CI, 1.35–6.48), and white women (OR, 2.41; 95% CI, 1.15–5.07).

Association between HAART use and healthcare utilization: results of population-based analytic approach

Results of the population-based approach were concordant with the results of the individual logistic regression models with respect to both emergency room visits and hospitalizations. We did not detect an association between HAART-use era and the proportion of women reporting more than three primary care visits.

Compared with emergency room use during the low HAART-use era, a lower proportion of HIV+ women without AIDS reported more than one emergency room visit per 6 months in the moderate HAART-use era (OR, 0.70; 95% CI, 0.53–0.93), the early high HAART-use era (OR, 0.75; 95% CI, 0.61–0.92) and the established high HAART-use era (OR, 0.79; 95% CI, 0.64–0.98). We found similar patterns of results among women who developed incident AIDS during the study, and women who had AIDS at the baseline study visit. Among women with incident AIDS, the reduction in emergency service use reached statistical significance only in the established HAART-use era (OR, 0.61; 95% CI, 0.39–0.96). Among women with AIDS at baseline, the proportion with emergency service use was significantly lower in the moderate HAART-use era (OR, 0.71; 95% CI, 0.54–0.93) and the early high HAART-use era (OR, 0.78; 95% CI, 0.62–0.98).

A lower proportion of women reported more than one hospitalization per 6 months as HAART prevalence increased over time, however these associations reached statistical significance only in the established high HAART-use era (compared with the low HAART-

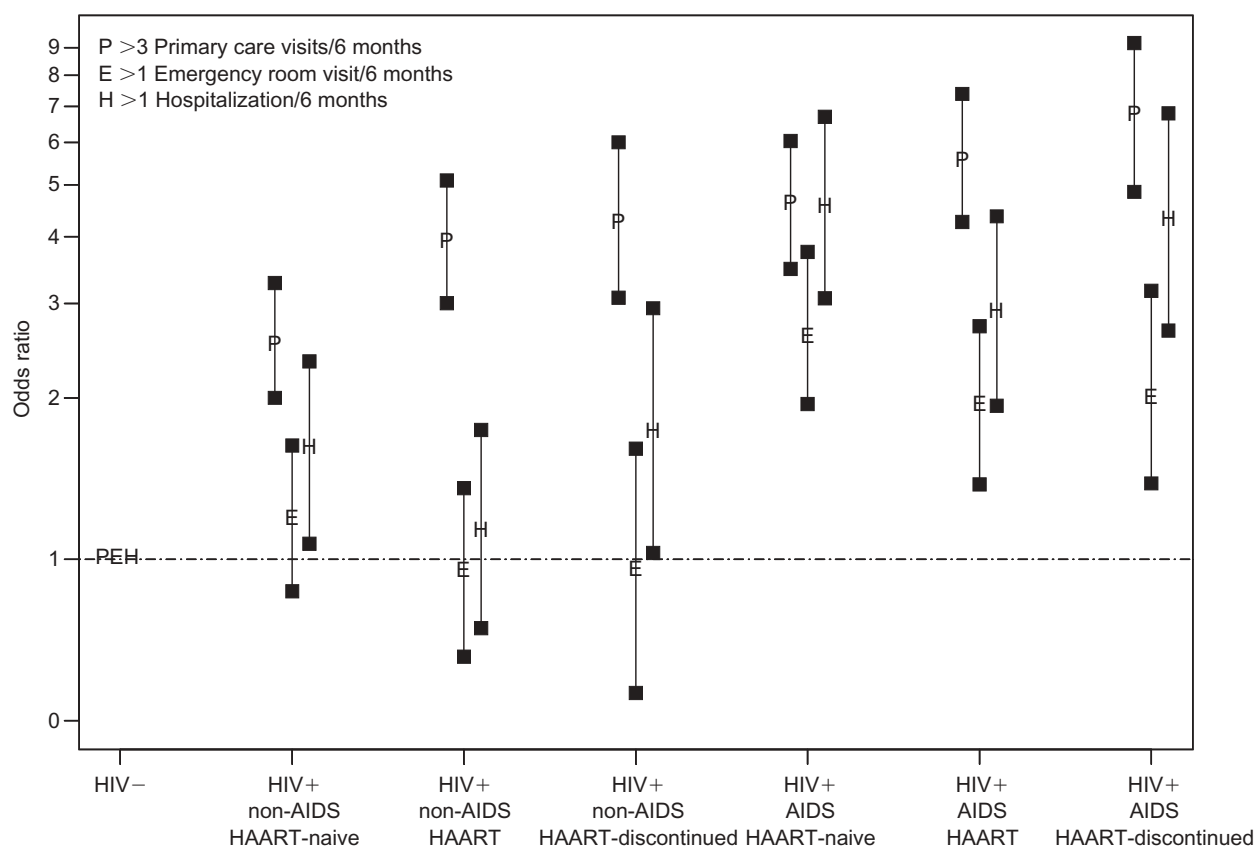


Fig. 1. Odds ratios (odds in favor of > 3 primary care provider visits, or > 1 emergency room visit, or > 1 hospitalization per 6 months) obtained from a multivariate logistic regression model, for groups of HIV-positive non-AIDS individuals with CD4 cell counts of $350 \times 10^6/l$ and HIV RNA of 10 000 copies/ml, and for groups of AIDS individuals with CD4 cell counts of $150 \times 10^6/l$ and HIV RNA of 50 000 copies/ml, relative to the HIV-negative group. The odds ratios in the plot are in the natural log scale and the vertical bars are their corresponding 95% confidence intervals.

use era) among HIV+ women without AIDS (OR, 0.69; 95% CI, 0.54–0.88), and in both the moderate HAART-use era (OR, 0.51; 95% CI, 0.37–0.71) and the established high HAART-use era (OR, 0.70; 95% CI, 0.54–0.92) among women with AIDS at the baseline visit.

We did not observe any changes over time in health services use among HIV-negative women.

Discussion

We explored the association between HAART and utilization of healthcare services. Our study has at least four important aspects. First, the WIHS is an ongoing large epidemiological cohort study and therefore has had time to accumulate experience that extends beyond the phase of early HAART introduction. The availability of data collected several years after the introduction of HAART is important as some earlier ecologic

studies suggested that there might be a slowing or reversing of the initial decreases in hospitalization rates observed after the introduction of HAART [20,22]. A second important aspect of our study is that we were able to model the impact of HAART use on healthcare service use relative to that of a comparison group of HIV-negative women enrolled in the WIHS. Third, to the best of our knowledge ours is the first report that specifically explores the relationship between HAART discontinuation (as distinct from the effect of HAART use) and the frequency of health service use among HIV-infected adults in the USA. As a proportion of treated individuals discontinue HAART (e.g., because of side effects, drug–drug interactions, virologic failure, drug holidays, etc.) it is important to study the health utilization patterns of this group. While our study did not permit analyses of subgroups of discontinuers by reason for discontinuation, it does offer some insights as to the healthcare use patterns in the group as a whole. Lastly, we present findings from two complementary analytic approaches, an individual approach and a population-based approach. Each analytic approach has

Table 4. Adjusted^a odds ratios^b of healthcare service utilization for highly active antiretroviral therapy (HAART) or HAART-discontinued versus HAART-naïve Stratified by health insurance status, employment status, and ethnicity.

Total study population Stratified population	Person-visits (%)				> 3 visits to primary care provider/6 months		1 visit to emergency room/ 6 months		> 1 hospitalization/6 months	
	HIV+ HAART- naïve	HIV+ HAART	HIV+ HAART- discontinued	HAART versus HAART-naïve	HAART- discontinued versus HAART- naïve	HAART versus HAART-naïve	HAART- discontinued versus HAART- naïve	HAART versus HAART-naïve	HAART- discontinued versus HAART- naïve	
	2207	1488	525	1.38^c	1.57	0.75	0.79	0.67	0.99	
Unemployed uninsured	284	145	60	2.95	3.01	0.73	0.76	0.65	0.86	
Unemployed insured	1351	853	324	1.30	1.51	0.76	0.66	0.66	0.93	
Employed uninsured ^d	102	77	17	1.17	1.72	0.43	0.71	2.03	NA	
Employed insured	448	396	117	1.67	1.91	1.11	1.89	1.35	2.96	
African-American	1368	704	255	1.43	1.59	0.78	0.75	0.73	0.80	
Latina	453	427	191	1.43	1.68	0.84	1.08	0.80	1.41	
White	330	312	62	1.10	1.36	0.90	0.89	0.64	2.41	

^aAdjusted by CD4 cell count and HIV RNA level. ^bOdds Ratios obtained from a multiple logistic regression model in which we assumed that the effect of HAART for the non-AIDS and AIDS groups were the same. ^cNumbers in boldface are significant at $\alpha = 0.05$. ^dAmong 17 employed uninsured HIV+ HAART-discontinued person-visits, no one had > 1 hospitalization/6 months

its own strengths and limitations, and the similar results yielded by the two approaches suggest that our findings are robust.

We found that women who were receiving HAART or who had discontinued HAART were more likely to report more than three primary care visits than were women who were HAART naïve. These associations were observed across multiple insurance/employment strata and ethnic strata. We do not feel that this association reflects higher background use of primary care services among women who eventually used HAART because the proportion of women with one to three primary care visits per 6 months among HAART-naïve women was similar to that among HAART users (Table 2).

Several studies have taken a population-based (ecological) approach to evaluating outpatient visits [11,12] and/or costs [12,15,17,20,21] as an outcome of HAART. The results from these reports have been conflicting. For example, a study conducted at a private hospital in New York City showed a 33% increase in outpatient visits made by HIV-positive patients from 1995 to 1996 [11]. Outpatient visits as defined in this study included multiple visit types (such as HIV counseling and testing) [11] and therefore it was difficult to draw conclusions about the trajectory of primary care use from these results. In contrast to the New York Study [11], a study of the Dallas (Texas) Veterans Affairs Medical Center found that number of HIV clinic visits per 100 HIV patients seen decreased by about 28% between 1995 and 1997 [12]. A report from a national probability sample of HIV-infected adults in medical care in the USA found that outpatient costs decreased between 1996 and 1998 [20]. In a response to a Letter to the Editor [38], however, the authors provided additional information that 'outpatient costs' as presented in the original paper represented the net costs of routine outpatient care (which had actually increased) combined with emergency department care (which had decreased) [39]. One study of health-care use in 1999 found that non-use of HAART was associated with higher outpatient utilization (excluding emergency room use) in a multivariate analyses [23].

Several ecologic studies found hospitalization rates and/or costs decreased over time soon after the introduction of HAART [11-17,20,22,23]. A limited number of studies compared HAART users to non-users; investigators at the Johns Hopkins University AIDS Service [21,22] and within the HIV Research Network [23] found that HAART use was associated with decreased hospital use.

With respect to emergency room visits, investigators from ecological studies at the Dallas Veterans Affairs

Medical Center found that emergency room visits declined after the introduction of HAART [12,15].

In our study, the proportion of HAART users reporting over one emergency room visit per 6 months was lower than that among HAART-naïve women, as was the proportion of HAART users reporting more than one hospitalization per 6 months. Of note, discontinuation of HAART was not associated with a reduction in emergency room use or hospitalization. Indeed, among the employed insured subgroup and the white subgroup, discontinued HAART was associated with a statistically significant increase in the probability of more than one hospitalization (compared with HAART naivety). We speculate that employed women may not be as easily able to schedule routine or urgent visits during business hours, and therefore management of HAART complications may require emergency room or hospital services. Future studies may collect data that permit testing of this hypothesis.

Although a large ethnically and geographically diverse cohort, the WIHS is limited to adult women and therefore may have limited generalizability to some HIV-infected subpopulations. However, unlike recruitment for the only national probability cohort of HIV-infected adults in the USA (which was exclusively among persons with regular medical care) [40], the WIHS captured women who were outside of medical care systems and therefore may be more representative of certain subpopulations of HIV-infected persons. Another limitation of our study is that we do not use data on medication adherence throughout this study, therefore persons classified as 'HAART users' may or may not have been taking these medications consistently. This misclassification however, would have tended to bias us toward the null, and therefore the associations we found between HAART use and healthcare utilization are likely to be underestimated in this report. We do not have detailed information regarding the reasons for discontinuation of HAART among study participants. In terms of what is currently understood about the pharmacological effects of HAART, either discontinuation because of side effects or discontinuation due to resistance might be expected to eventually result in clinical deterioration (the former due to removal of viral suppression, the latter due to failure to achieve/sustain viral suppression). Thus, we feel our ability to assess the effects of HAART discontinuation on subsequent healthcare utilization is not substantially hindered by the inability to determine reasons for HAART discontinuation.

Results of earlier studies examining temporal trends have been intriguing and suggested that close attention to the long-term 'post-HAART' era is warranted. Our study supports the hypothesis that the decrease in use of emergency room and inpatient hospital services is

attributable to HAART. Our findings suggest that HAART users continue to enjoy this benefit (compared with the HAART-naïve) several years into the HAART era. Furthermore, our study provides evidence that this reduction in hospitalization and emergency room use is not sustained in persons who discontinue HAART use.

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Appendix

Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (K. Anastos); Brooklyn, NY (H. Minkoff); Washington DC Metropolitan Consortium (M. Young); The Connie Wofsy Study Consortium of Northern California (R. Greenblatt, P. Tien); Los Angeles County/Southern California Consortium (A. Levine); Chicago Consortium (M. Cohen); Data Coordinating Center (S. J. Gange).