PUBLIC HEALTH POLICY AND PRACTICE

Effectiveness of highly active antiretroviral therapy among HIV-1 infected women

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Study objective: To describe the impact of highly active antiretroviral therapy (HAART) on mortality, morbidity, and markers of HIV disease progression in HIV infected women.
Design: Data collected from the Women's Interagency HIV Study, a prospective cohort study that enrolled women between October 1994 and November 1995.
Setting: Six clinical consortia based in five cities in the United States (New York, NY; Washington, DC; Los Angeles, CA; San Francisco, CA; and Chicago, IL).
Participants: A total of 1691 HIV seropositive women with a study visit after April 1996.
Main results: Beginning in April 1996, the self reported use of HAART increased over time, with more than 50% of the cohort reporting HAART use in 1999. There was a 23% decline per semester in the incidence of AIDS from April 1996 (95% confidence intervals (CI) −29% to −16%). Furthermore, there was a 21% decline of the semiannual mortality rates among those with AIDS at baseline (95% CI −27% to −14%) and an 11% decline among those AIDS free at baseline (95% CI −3% to −18%). CD4+ lymphocyte counts either increased (women with baseline AIDS) or stabilised (women without baseline AIDS) after April 1996, and HIV RNA levels dramatically declined in both groups, although the percentage of women with HIV RNA above 4000 cps/ml remained stable at approximately 40% since mid-1997.
Conclusions: Despite concerns regarding the use of antiretroviral therapies in this population, the use of therapies led to improved immunological function, suppressed HIV disease activity, and dramatic declines in morbidity and mortality.

Beginning in the mid-1990s, significant advances have been made in the treatment of human immunodeficiency virus type 1 (HIV) infection, and new antiretroviral nucleoside reverse transcriptase inhibitors (RTIs) are now routinely used in combination with potent protease inhibitors and non-nucleoside RTIs. The efficacy of these highly active antiretroviral therapies (HAART) has been demonstrated in numerous clinical trials,[1–3] but observational studies of HIV infected populations provide the opportunity to supplement and complement these findings in two ways.[4] Firstly, similar to clinical trial analyses, observational data can be used to compare outcomes among individuals reporting and not reporting use of therapies. These analyses provide measures of individual effectiveness among a population that is generally larger, followed up for a longer duration, and comprised of participants who are more representative of existing patient populations. Therapies in observational studies, however, are not randomised as in clinical trials, and their use is dependent on a variety of demographic[5][6] and health related factors that are indications for treatment.[7] These analyses, while important for supplementing the findings of clinical trials, are therefore vulnerable to residual confounding because of unmeasured factors leading to the use or prescription of various therapies, and sophisticated multivariate analyses are required to draw correct inferences.[8–12]

In contrast with measuring the effect of therapies at the individual level, a second approach is to estimate the effectiveness of therapies at the population level. This approach measures the impact of an intervention by examining the reduction of mortality or changes in markers before and after its introduction. Population effectiveness in cohort studies capitalises on the longitudinal collection of data and compares cohort outcomes in different time periods.[4][13–15] This analysis requires that trends in the use of treatment and other relevant factors be carefully documented to rule out alternative explanations for observed differences in the outcomes under study, and is most convincing when new therapies become available and widely used at an identifiable point in time. The comparisons in the occurrence of disease and trends in disease markers provide a relevant and important public health perspective: effectiveness measures the overall changes in population health, reflecting the net effect of all factors that influence access, prescription, efficacy, adherence, discontinuation and development of potential resistance to therapies.

A number of prior studies have documented the effectiveness of different HIV therapies in reducing mortality and the incidence of AIDS in different populations[11][16–22] as well as increasing the time after an AIDS diagnosis.[23][24] Few of these studies, however, have focused specifically on the long term effectiveness of HAART in women and ethnic minorities, the populations in which HIV has expanded in recent years in the United States.[25–28] Epidemiological analyses have shown that women and minorities now represent 67% of newly diagnosed AIDS cases, 62% of people living with AIDS, and 69% of newly reported diagnoses of HIV infection.[27][28] Differences in the response to HAART among these populations has been reported by some groups[29][30] but not others.[23][24] The basis for these differences is likely to be multifactorial. Firstly, the response to HAART may be different because of biological factors. Viral load differences have been documented between

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men and women at higher CD4+ lymphocyte counts,[31–33] although the physiological basis for these differences is unclear. Gender-based differences in either viral replication rates or decay rates may explain these viral load differences, as the steady state of viral load is reached rapidly.[34 35] If these differences exist, they may have implications for how effective therapies are at reducing viral levels in women compared with men. One possible explanation for the gender-based differences is the difference in hormonal milieu. Sex steroids such as oestrogens and progestins are important modulators of immunological activity and thus could plausibly influence host responses to HIV infection and HIV replication rate. Greenblatt et al[36] have recently reported the influence of ovulatory cycle phase on plasma HIV RNA level, with significantly lower levels occurring in the midluteal compared with the early follicular cycle phase.

Furthermore, HIV infected women and minorities are more likely to have a lower socioeconomic status,[37] which may have a number of consequences affecting the effectiveness of HAART, including lower adherence to treatment[38] and different utilisation patterns of antiretroviral therapy (ART).[39] Access to health care may also play an important part,[39 40] because health coverage is not universal in the United States and dependent on access to public and private health insurance. However, it has been shown that the Ryan White CARE Act of 1990, a federal assistance programme whose goal is to help HIV infected people overcome financial barriers to accessing HIV medical care, has seemed to equalise access to medical services for women and minorities.[41]

In this report, we investigate the effectiveness of HAART in the Women's Interagency HIV Study (WIHS), an ongoing cohort study of HIV infected women and women at risk for HIV infection. The demographics of the WIHS cohort closely mirror the characteristics of HIV infected women in the general US population[42] and clinical care is provided in a variety of settings. A more complete discussion of the trends in ART and predictors of HAART usage in the WIHS have been presented elsewhere.[5 7] In this report, we document longitudinal trends in mortality, self reported clinical AIDS, and markers of HIV disease progression (CD4+ lymphocyte count, and plasma HIV RNA) in this representative cohort, to contribute to the understanding of the public health impact of these new potent treatments.

METHODS
Subjects and Design
The WIHS is an ongoing prospective study of HIV-1 infection in women, conducted in five locations within the United States: New York City (two sites), Washington DC, Chicago, Southern California and the San Francisco Bay area. The WIHS methods and baseline cohort characteristics have been described previously.[42] Briefly, from October 1994 to November 1995, 2628 women (2059 HIV-1 seropositive and 569 seronegative) were enrolled in WIHS. Women were recruited from HIV primary care clinics, hospital-based programmes, research programmes, community outreach sites, women's support groups, drug rehabilitation programmes, HIV testing sites, and referrals from enrolled participants. The HIV infected and uninfected women were recruited from similar sources and were matched on demographic and risk factors for acquisition of HIV infection. Every six months, WIHS participants were interviewed using a structured questionnaire, received physical and gynaecological examinations, and provided multiple laboratory specimens. In this report, AIDS defining clinical conditions (consistent with 1993 CDC clinical surveillance conditions, but excluding immunological based criteria of low CD4),[43] were ascertained through self report. Participants' deaths were ascertained continuously using a combination of active (for example, death certificate abstraction upon notification of a participant's death) and passive (for example,

national death registry searches) surveillance methods. After five years, the overall retention rate in the WIHS was approximately 81%.[44]

Quantification of HIV-1 RNA in plasma was performed using the isothermal nucleic acid sequence based amplification (NASBA/Nuclisens) method (Organon Teknika, Durham, NC) in laboratories participating in the NIH/NIAID, Virology Quality Assurance Laboratory proficiency testing programme. The lower limit of quantification through 9/97 was 4000 copies/ml using a 0.1 ml sample input; from 10/97 through 12/98 the lower limit was 400 copies/ml using 0.2 ml sample input; after 1/99 the lower limit was 80 copies/ml using 1.0 ml sample input. Lymphocyte subsets were quantified using standard flow cytometric methods in laboratories participating in the NIH/NIAID Flow Cytometry Quality Assessment Program.

At each study visit, self reported ART use in the period since the previous visit was assessed by interviewers stating the name of each drug, both by brand and generic drug name, and showing participants photomedication cards. For this analysis, we focused on the three classes of FDA approved therapies: nucleoside RTIs, including zidovudine, stavudine, zalcitabine, didanosine, and lamivudine; protease inhibitors, including saquinavir, indinavir, ritonavir, and nelfinavir; and non-nucleoside RTIs, including nevirapine and delavirdine. HAART was defined according to the 1997 Department of Health and Human Services guidelines[45] as two or more nucleoside RTIs with either a protease inhibitor or a non-nucleoside RTI. Women taking a protease inhibitor plus zidovudine and stavudine, however, were classified as receiving non-HAART combination therapy, as indicated by the treatment guidelines.

Because of the interest in evaluating longitudinal trends in immunological and virological markers surrounding the introduction of HAART, we restricted our analysis of markers to HIV seropositive participants who had at least one WIHS study visit after 1 April 1996. This date was chosen as the approximate time when HAART became available to women in this cohort. With this restriction, we minimise capturing any longitudinal trends in markers that occurred because of cohort drop out or death before HAART was available.

Statistical analysis
Data were categorised into six month calendar time intervals: 10/94–3/95, 4/95–9/95, 10/95–3/96, 4/96–9/96, 10/96–3/97, 4/97–9/97, 10/97–3/98, 4/98–9/98, and 10/98–3/99. The incidence of mortality and AIDS defining illnesses (self reported) was computed for each time interval and was constructed from the number of deaths or reported AIDS cases divided by the total number of person years of observation in the six month period. The temporal trends in the incidence of AIDS and death were evaluated using log-linear (Poisson) regression models.[46]

Longitudinal changes in CD4+ and CD8+ lymphocyte counts through 9/99 were modelled using linear random effects regression.[47] Segmented linear regression models were used to facilitate comparisons of marker trajectories before

Table 1 Baseline characteristics of WIHS participants with at least one study visit after 1 April 1996. Characteristics that do not sum to category totals are because of missing values

	Self reported AIDS at baseline (n=492)	No self reported AIDS at baseline (n=1199)
Median age in years (range)	38 (20–62)	36 (17–73)
Race/ethnicity		
White	95 (19%)	205 (17%)
Black	277 (56%)	666 (56%)
Hispanic	108 (22%)	295 (25%)
Other	12 (3%)	30 (2%)
Education less than high school	185 (38%)	446 (37%)
Annual household income		
≤$12000	318 (66%)	717 (62%)
Risk category		
Injection drug use	199 (41%)	378 (32%)
Heterosexual risk	181 (37%)	510 (43%)
Transfusion risk	23 (5%)	42 (3%)
Risk not unidentified	82 (17%)	258 (22%)
CD4+ lymphocyte counts (cells/mm³)		
Mean (standard deviation)	336.1 (272.1)	429.9 (281.4)
<200	171 (36%)	224 (19%)
200–500	195 (41%)	573 (49%)
≥500	107 (23%)	364 (31%)
HIV-1 RNA (copies/ml)		
Median (interquartile range)	31500 (5500–130000)	14000 (<4000–62500)
≤4000	370 (77%)	762 (65%)

and after the time when HAART was introduced in the cohort (4/96). That is, linear models were used to summarise marker trajectories over time, but the slopes of the markers obtained before 4/96 were allowed to be different from the slopes of the markers obtained after 4/96. We also investigated models for square root transformed CD4+ and CD8+ lymphocyte counts, but the results were similar to those obtained using the untransformed data. Because of the relatively high limit of plasma HIV RNA quantification (4000 cps/ml) in early samples, we analysed trends in the prevalence of detectable HIV RNA (>4000 cps/ml). Generalised estimating equation (GEE) methods [48] were used with a binary response of whether HIV RNA was detectable and with time as a continuous predictor. Similar to the lymphocyte data, the observed slopes in the prevalence of undetectable HIV RNA before and after 4/96 were compared while adjusting for the correlation among repeated measurements from the same person.

RESULTS
Of the 2059 HIV positive women enrolled in the WIHS, 692 reported AIDS defining clinical conditions at their baseline

visit (10/94–11/95). Seventy one per cent of the women with clinical AIDS at baseline (n=492), and 88% of the women without clinical AIDS at baseline (n=1199), participated in a study visit after 1 April 1996. Table 1 describes selected baseline demographic characteristics of these women. The median age of the cohort was in the mid-30s, and a majority of participants were African-American and with an annual household income less than $12 000. Most women reported risk exposures from either injecting drugs or through heterosexual contact (with a man at high risk for HIV infection). Women reporting AIDS conditions at baseline had lower CD4+ lymphocyte counts and higher HIV RNA levels.

At enrollment, approximately 35% of HIV positive women reported current use of any prescription ART, which for the majority comprised monotherapy (78%). During the final period under study (3/99–9/99), reported current use of any ART increased to 69% overall. With the introduction of protease inhibitors and non-nucleoside RTIs, the number of women reporting current use of HAART between 3/99 and 9/99 increased to approximately 50% (table 2). The majority of women on HAART reported use of one protease inhibitor with

Table 2 Longitudinal trends of reported use of highly active antiretroviral therapy (HAART), incidence of self reported clinical AIDS, and mortality

	Number reporting use of HAART (%)			Mortality rate*	
Time period	AIDS at baseline	AIDS free at baseline	AIDS incidence rate*	AIDS at baseline	AIDS free at baseline
4/95–9/95	5 (1.1%)	4 (0.4%)	12.09 (57/471.4)	19.47 (41/210.6)	2.19 (11/502.8)
10/95–3/96	8 (1.8%)	9 (0.8%)	13.74 (74/538.7)	23.22 (59/254.1)	4.96 (30/604.3)
4/96–9/96	44 (9.3%)	85 (7.1%)	14.50 (72/496.4)	16.92 (40/236.4)	3.58 (21/586.8)
10/96–3/97	133 (30.2%)	261 (25.1%)	12.85 (58/451.4)	12.18 (27/221.7)	4.24 (24/565.9)
4/97–9/97	163 (39.6%)	387 (37.3%)	8.48 (36/424.3)	11.35 (24/211.4)	2.91 (16/548.9)
10/97–3/98	189 (49.2%)	428 (42.2%)	6.23 (25/401.0)	9.69 (19/196.0)	3.03 (16/528.4)
4/98–9/98	159 (43.9%)	415 (43.7%)	4.47 (17/380.1)	5.90 (11/186.4)	2.54 (13/511.0)
10/98–3/99	167 (49.9%)	479 (51.2%)	5.07 (18/354.9)	6.32 (11/174.0)	2.46 (12/486.9)
Overall change per semester			−14%	−17%	−5%
95% CI			−18% to −10%	−22% to −12%	−12% to +2%
Change per semester after 4/96			−23%	−21%	−11%
95% CI			−29% to −16%	−27% to −14%	−18% to −3%

*AIDS incidence rate and mortality rates are reported in terms of 100 person years (number of events/total person years).

Table 3 Mean level and annual change in CD4+ and CD8+ lymphocyte counts before and after 4/96. 95% Confidence intervals are given in parentheses

	Self reported AIDS at baseline	No self reported AIDS at baseline
CD4+ lymphocyte count (cells/mm³)		
Mean level in 4/96	310.2 (288.2 to 332.1)	404.8 (390.3 to 419.3)
Slope per year 10/94–4/96	−19.4 (−32.9 to −5.9)	−13.0 (−22.2 to −3.7)
Slope per year 4/96–9/99	7.2 (2.7 to 11.7)	1.1 (−2.0 to 4.1)
Difference of slopes*	26.6 (10.3 to 42.9)	14.1 (4.1 to 24.1)
CD8+ lymphocyte count (cells/mm³)		
Mean level in 4/96	863.2 (813.0 to 913.4)	940.5 (913.0 to 967.9)
Slope per year 10/94–4/96	6.5 (−29.2 to 42.3)	37.3 (17.1 to 57.4)
Slope per year 4/96–9/99	−12.5 (−24.6 to −0.6)	−22.1 (−28.8 to −15.5)
Difference of slopes*	−19.1 (−62.3 to 24.1)	−59.4 (−83.8 to −35.0)

*Represents post 4/96 slope – pre 4/96 slope.

two or more nucleoside RTIs (54%). Among all women receiving HAART, the most commonly reported protease inhibitors between 4/99 and 9/99 were nelfinavir (38%) and indinavir (24%); the most common nucleoside RTI combination was zidovudine/lamivudine (31%). The reported use of these agents began to increase shortly after their approval by the FDA.

Other medications used to treat or prevent opportunistic infections also significantly increased over the period of study. The reported use of *Pneumocystis carinii* pneumonia (PCP) therapies (Bactrim (TMP-SMX), dapsone, pentamidine, atovaquone, daraprim, clindamycin, primaquine, trimextrate, and fansidar) from before to after 4/96 increased from 54% to 61%. Over the same period, antimycobacterial treatment (azithromycin, cripo, clarithromycin, clofazimine, amikacin, rifabutin, ethambutol, isoniazid, rifampin, and pyrazinamide) increased from 12% to 22%, acyclovir use increased from 15% to 30%, and antifungal therapy (ketoconazole, itraconazole, and fluconazole, ampho B, nystatin, mycelex, monistat, and terazol) increased from 31% to 44%.

Table 2 details the trends in reported clinical AIDS (among women not reporting AIDS at baseline) and mortality in six month intervals. During the course of follow up, the incidence of clinical AIDS showed a slight (although non-significant) rise over the first year 4/95 to 3/96 (12.09 to 14.50 cases per 100 person years), but then showed a significant 14% semiannual decline over time to 5.07 cases per 100 person years between 4/98 and 3/99. When excluding the data prior to 4/96, the estimated decline was 23% per semester. The most common AIDS defining condition reported in both the first and last intervals was oesophageal candidiasis.

The overall mortality rate also declined over the course of follow up (table 2). The mortality rate among the women reporting clinical AIDS at baseline was much higher than for those not reporting clinical AIDS at baseline. The mortality rate showed a strong, significant decline by 17% per semester among those reporting clinical AIDS at baseline from 4/95 to 3/99. In contrast, the mortality rate over the same time period among those women not reporting clinical AIDS at baseline did not show a statistically significant decline (−5% per semester). When excluding the data in the first year (4/95–3/96), however, there was a statistically significant 11% semiannual decline in mortality between 4/96 and 3/99.

Table 3 describes the longitudinal trends estimated using random effects models for CD4+ and CD8+ lymphocyte counts among those with at least one visit after 4/96. The women reporting clinical AIDS at baseline had lower mean levels of both markers throughout the entire follow up period. The annual CD4+ decline of 19.4 cells/mm³ per year before 4/96 improved to a 7.2 cells/ mm³ annual increase between 4/96 and 9/99. The CD8+ slope in the period before 4/96 was not distinguishable from zero, nor from the CD8+ slope between 4/96 and 9/99, but did decline in the latter period by 12.5 cells/year (95% CI −24.5 to −0.6). Qualitatively similar trends were found among the women not reporting clinical AIDS at baseline. The annual CD4+ decline of 13.0 cells/mm³ per year before 4/96 also changed to a 1.1 cells/ mm³ annual increase after 4/96. CD8+ increases before 4/96, and declines after 4/96 were larger in magnitude and significance.

The contrast of the greater CD4+ increases among those with AIDS as compared with those not reporting AIDS at baseline was investigated further by stratifying the AIDS free

Table 4 CD4+ Lymphocyte characteristics and HAART use of AIDS free women stratified by baseline CD4+ lymphocyte count

Time period	Baseline CD4 <200 (n=224)		200 ⩽ Baseline CD4 <500 (n=573)		Baseline CD4 ⩾500 (n=364)	
	HAART use	Mean CD4 (cells/mm³)	HAART use	Mean CD4 (cells/mm³)	HAART use	Mean CD4 (cells/mm³)
10/94–3/95	1.4%	112	0.0%	344	0.0%	733
4/95–9/95	0.5%	116	0.6%	361	0.0%	703
10/95–3/96	2.0%	96	0.9%	352	0.0%	696
4/96–9/96	16.8%	125	5.9%	358	3.0%	664
10/96–3/97	52.9%	151	23.4%	372	11.1%	684
4/97–9/97	61.7%	173	39.1%	369	19.0%	595
10/97–3/98	62.3%	188	46.8%	358	23.8%	618
4/98–9/98	63.1%	211	46.7%	370	28.7%	607
10/98–3/99	66.0%	231	56.0%	383	35.7%	592
4/99–9/99	73.9%	223	59.7%	388	35.0%	586
CD4+ slope per year 10/94–4/96*		4.6 (−9.2 to 18.4)		2.7 (−8.5 to 13.8)		−58.8 (−80.4 to −37.3)
CD4+ slope per year 4/96–9/99*		35.6 (30.6 to 40.5)		8.6 (5.0 to 12.3)		−27.8 (−34.6 to −21.0)
Difference of slopes*†		31.0 (13.9 to 48.1)		5.9 (−7.5 to 19.3)		31.0 (5.2 to 56.8)

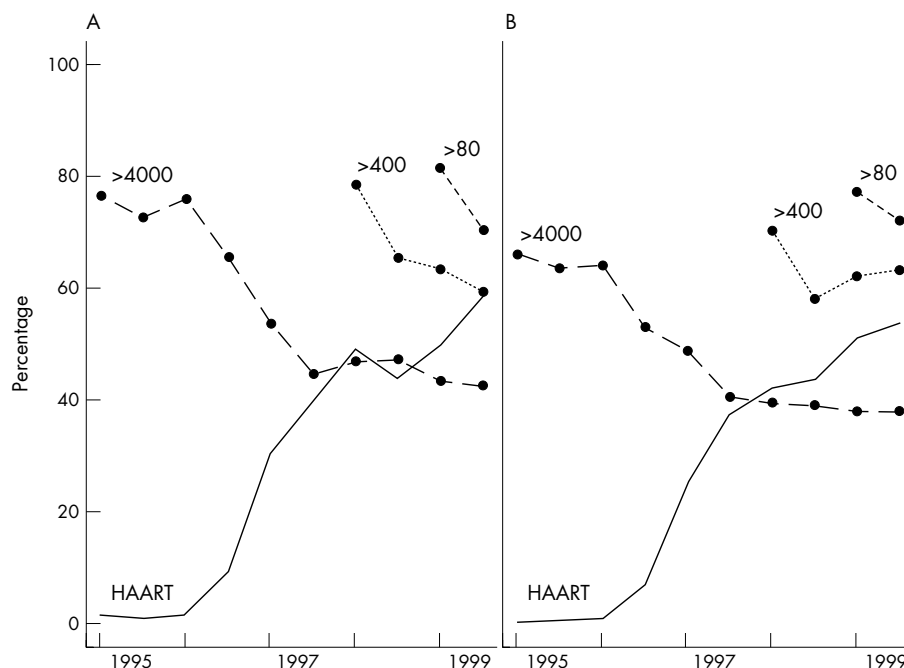*95% Confidence intervals in parentheses; †represents post 4/96 slope – pre 4/96 slope.

Figure 1 Temporal trends in plasma HIV RNA among women with (A) and without (B) self reported AIDS at baseline. The solid lines without points depict the percentage of women reporting HAART. The lines with points describe the percentage of women with HIV RNA above 4000 cps/ml (solid lines) throughout the entire follow up period, and the percentage above 400 cps/ml (dotted lines) and 80 cps/ml (dashed lines) at later times when more sensitive assays were used. Data are plotted at midpoint of calendar.

women by their baseline CD4+ lymphocyte count (table 4). The women with lower CD4+ lymphocyte counts were more likely to receive HAART when it became available, consistent with our prior reports documenting selection by indication effects.[7] The response to treatment was different for each CD4+ strata, with those women in the lowest CD4+ strata showing the best overall trends in CD4+ response after 4/96 (+35.6 cells/year). Furthermore, the women with the highest CD4+ lymphocyte counts, and the lowest reported use of therapy, showed a decline after 4/96 (−27.8 cells/year) that was significantly slower than the decline prior to 4/96 (−58.8 cells/year).

Figure 1 depicts changes in plasma HIV RNA and changes in HAART, stratified among those women with AIDS at baseline (fig 1A) and those without AIDS at baseline (fig 1B). The figure describes the percentage of women with HIV RNA above 4000 cps/ml throughout the entire follow up period, and the percentage above 400 cps/ml and 80 cps/ml at later times when more sensitive assays were used. Prior to 4/96, the percentage of samples that were above 4000 cps/ml was unchanged, and the women reporting clinical AIDS at baseline had a higher percentage with HIV RNA (75%) above 4000 cps/ml than those women not reporting AIDS (64%). Beginning with the data collected after 4/96, the percentage of women above 4000 cps/ml dramatically declined in both groups up to mid-1997. After that time, this percentage was stable at approximately 40% for both groups.

DISCUSSION
This study showed a decline in mortality and self reported AIDS, as well as favourable trends in markers of HIV disease progression, over the time that HAART became available to women in the WIHS. These descriptions are important for evaluating how newly available therapies have had an impact on the clinical and laboratory manifestations of HIV-1 infection in a population-based setting outside of clinical trials. Prospective cohort studies that comprehensively characterise a broad range of people over time provide the ideal setting to describe these trends. Our cohort is closed to

enrollment of new individuals; thus, without treatments, the natural history of HIV infection would provide an expectation that the average CD4+ cell counts decline and AIDS incidence and mortality increase. Taken in this context, the attenuation of marker decline over time and reducing incidence of clinical outcomes are even more significant.

From a public health perspective, it is particularly important to record changes in HIV related clinical outcomes in women who reflect recent demographic characteristics of HIV infection in the United States, have more severe disease, and are receiving HAART. Consistent with a number of prior reports, the results of our study show trends in women that are both qualitatively and quantitatively similar to the trends described in HIV infected men. For example, in the HIV outpatient study that consisted of participants with CD4+ lymphocyte counts below 100 cells/mm^{3}, the mortality rate declined from 29.4 in 1995 to 8.8 cases per 100 person year in 1997.[18]

Our study is one of the first, however, to describe the dramatic population level changes in HIV RNA levels occurring with the introduction of HAART. The high proportion of WIHS women with HIV RNA levels below the NASBA limit of detection used in this study (4000 copies/ml) indicates a potential benefit of retesting using more sensitive HIV RNA assays. The multi-year −70°C storage of plasma in the WIHS for ongoing retesting with more sensitive assays demonstrates the utility of maintaining specimens in anticipation of future advances in technology.

As shown in table 4, the strongest CD4+ lymphocyte responses occurred among those who began with the lowest CD4+ lymphocyte counts. Because of the "selection by indication" effects determining who receives treatment,[7] this group also had the highest proportion using HAART. The improvements in CD4+ lymphocyte counts in this group are consistent with changes reported by others in controlled studies of people with very low CD4+ lymphocyte counts[49]; little clinical data exist for comparing the changes among those with less impaired immune systems. However, our data show the public health impact of treatments when administered in the population, complementing the findings from

clinical trials. HAART use of up to 60% among those with CD4+ lymphocyte counts between 200 and 500 at baseline led to negligible changes in CD4+ trajectories; among those with counts above 500, CD4+ lymphocyte counts continued to decline, although at a slower rate. CD4 slopes before April 1996 may underestimate the rate of change in the general population, as we have excluded women with the most rapid rates of CD4 decline who died before the introduction of HAART.

The HIV RNA trends in 1997 to 1999, and the stabilisation of AIDS incidence and mortality rates after April 1998, show that the largest impact of HAART in this cohort has perhaps already occurred. There exists a substantial pool of women who have not yet started HAART in the cohort because of a number of factors,[5] including that their disease has not yet progressed to the level that treatment is recommended, possible problems with access, and the women's decision to begin treatment. Individually, some of these women will benefit from initiating potent treatment early while others are likely to receive the optimal benefit from delaying the start of therapy. From a population perspective, women who are most ill and at highest risk for clinical disease and death have generally started treatment, expanding the use of HAART is likely to have a less dramatic impact on reducing HIV RNA levels and on the incidence of clinical disease and death.

We have attributed much of the observed longitudinal improvement in lymphocyte subsets and viral RNA levels to the introduction and expanded use of HAART. However, alternative explanations may be possible. Firstly, the introduction of other treatments and changing patterns of use of existing therapies could account for some of the positive longitudinal trends. For example, stavudine was approved by the FDA in mid-1994, and lamivudine was approved in late 1995. Previously published reports have attributed improvements in survival time to the introduction of these drugs,[20] which occurred just before and, in part, concurrently with the introduction of protease inhibitors; these changes are therefore difficult to distinguish. We have also described increasing use of prophylaxis for opportunistic infections (that is, PCP, *Mycobacterium avium* complex, herpes simplex viruses and varicella zoster virus) in the same era as the expanded use of HAART, which might also account for some of the decline in the incidence of AIDS.

Other characteristics of this work relate to our use of self reported AIDS; confirmation of diagnoses via medical record abstraction and matching to AIDS registries is ongoing. Reviews of AIDS self reports with confirmations from registry data,[50] and the strong association of incident self reported AIDS with HIV RNA and CD4+ lymphocyte counts [51] provide encouraging evidence of the overall reliability of these self reported data. However, it is possible that some of the decline in self reported AIDS over time may be because of changes in reporting behaviour—either a decrease in overreporting or an increase in underreporting.

Participant survival bias could be another potential explanation for the observed declines in death and self reported AIDS. The initially high prevalence of AIDS and subsequent death would remove the least healthy individuals who have been infected the longest. The resulting cohort at later times would be substantially healthier, thereby leading to lower numbers of subsequent events.[52] One solution to this problem is to analyse data from a cohort of persons with a known date of HIV infection, and then take the time that has passed from infection to the date of study in consideration.[22] Unfortunately, observation of incident HIV infection is technically difficult, particularly in a population such as US women, among whom HIV infection is a relatively infrequent event. Recently, methods have been introduced to overcome the uncertainty in time of seroconversion through the use of information contained in disease progression markers[53]; investigations with WIHS data are continuing.

Lastly, we have not considered other important issues related to the use of antiretroviral therapy, such as access to care, adherence to treatment, and development of drug resistance. Most of the WIHS participants reported having medical insurance (including either government assisted public insurance, private insurance, or combinations) and having a primary care provider,[54] although the WIHS does not provide medical care beyond referrals for abnormal findings. This suggests that access to antiretroviral therapy among these women was not a major impediment to use. In the general population, however, there are often substantial barriers to care [54–56] that may account for some of the heterogeneity of survival times from AIDS.[23] Data on treatment adherence (T Wilson, *et al*, International AIDS Conference, Durban, South Africa 2000) and drug related resistance (RM Grant, *et al*, 5th Workshop on Drug Resistance and Treatment Strategies, 2001) in the WIHS are currently being investigated.

In summary, our data provide important and encouraging evidence that the public health gains seen in other populations of HIV infected people in the US are also experienced by HIV infected US women. It will be important to continue monitoring cohorts such as the WIHS for further trends in HIV disease outcomes as new therapies are approved and come into widespread use. Furthermore, cohort studies offer the opportunity to detect and track the occurrence of long term side effects (such as ART induced lipodystrophy) or treatment failure, perhaps as a result of the development of viral resistance. Follow up over longer time periods will be particularly important, as current clinical trials are of short (1–2 year) duration with little long term monitoring.

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