Published in final edited form as:

AIDS Care. 2012 January ; 24(1): 20–29. doi:10.1080/09540121.2011.592814.

Influence of gender on receipt of guideline-based antiretroviral therapy in the era of HAART

Jennifer M. Cocohoba, Pharm.D., MAS¹, Keri N. Althoff, PhD, MPH², Rebecca Godfrey, B.A., P.A.-C³, Frank J. Palella, MD⁴, and Ruth M. Greenblatt, MD^{1,5}

¹Department of Clinical Pharmacy, School of Pharmacy, University of California San Francisco

²Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

³John Hopkins Bloomberg School of Public Health

⁴Department of Medicine, Infectious Diseases Division, Feinberg School of Medicine, Northwestern University

⁵Departments of Medicine, Epidemiology and Biostatistics, School of Medicine, University of California San Francisco

Abstract

United States HIV treatment guidelines delineate preferred antiretroviral regimens (ART) and discourage use of subpotent, toxic, or adversely interacting combinations. It is unclear how often patients receive guideline concordant ART and what factors are correlated with receiving guideline-inconsistent ART. The objective of this study was to assess ART reported by participants of the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) to determine whether gender is associated with receipt of guideline-inconsistent ART. ART reported by WIHS and MACS participants from 1/1/2001 – 12/31/2007 was assessed for concordance with HIV guidelines. Logistic regression with generalized estimating equations estimated the crude and adjusted odds ratios and 95% confidence intervals associated with guideline-inconsistent regimens. Of 2937 participants, 463 subjects (WIHS n=263; MACS n=200) reported guideline-inconsistent ART during the study period. Age greater than 50 years (aOR = 2.22, 95% CI 1.14, 4.33) and HIV-1 RNA (aOR=1.17, 95% CI 1.08, 1.25) but not participant gender (aOR= 1.21, 95% CI 0.88, 1.65) were associated with guideline-inconsistent ART. The prevalence of guideline inconsistent ART peaked in 2004, however there was not a statistically significant increase or decrease over time. Guideline inconsistent ART was not related to gender, but was often used by older patients, and patients with higher viral loads. Monitoring ART quality based on concordance with expert guidelines could improve treatment outcomes in a substantial number of patients.

Keywords

antiretroviral; gender; guideline; concordance; treatment disparities

Introduction

Antiretroviral treatment (ART) strategies continue to evolve rapidly due to the introduction of convenient dosing formulations, improved adverse effect profiles, and drugs with novel mechanisms of action. As the antiretroviral formulary expands, preferred drug regimens that suppress viral replication, raise CD4 T-lymphocyte (CD4) counts, and minimize toxicity are determined through both clinical research and provider experience. Combinations that are less potent, result in excess toxicity, or have unsubstantiated effects are also determined. These optimal and suboptimal regimens are defined in expert HIV treatment guidelines published by the US Department of Health and Human Services (DHHS), which are updated frequently as new clinical information emerges. ("Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents," 2009)

Although HIV treatment guidelines are widely available, some groups may be at higher risk of receiving suboptimal ART. Women may be particularly at risk for ART disparities; previous studies have found that HIV-infected women in the U.S. and Canada were less likely to receive any ART or early ART, less likely to receive protease inhibitors, and frequently received initial ART regimens that were inconsistent with treatment guidelines. (Andersen et al., 2000; Cocohoba et al., 2008; Eisenman et al., 2007; Gebo et al., 2005; King et al., 2008; McNaghten, Hanson, Dworkin, & Jones, 2003; Mocroft, Gill, Davidson, & Phillips, 2000; Smith & Kirking, 1999) The objective of this study was to determine whether gender is associated with receiving guideline-inconsistent ART by comparing use of antiretroviral regimens as self-reported by women in the Women's Interagency HIV Study (WIHS) and men in the Multicenter AIDS Cohort Study (MACS). These large observational cohort studies provide an opportunity to look at real-world antiretroviral prescribing patterns in relation to a wide range of potentially influential social and demographic characteristics.

Methods

Study Populations

The WIHS is the largest prospective, observational cohort study of the natural and treated history of HIV in women in the US. Women were enrolled at 6 sites including Bronx, NY, Brooklyn, NY, Baltimore, MD/Washington D.C., Chicago, IL, the San Francisco Bay Area and Los Angeles, CA, during two recruitment waves in 1994–1995 (n=2,625 women) and 2001–2002 (n=1,143 women). Descriptions of the WIHS cohort and its methodology have been published previously. (Bacon et al., 2005; Barkan et al., 1998) WIHS participants undergo semi-annual study visits during which an extensive interview is administered including inquiries about socio-demographic characteristics, medical care, health status, mental and behavior health issues, and medication use. In order to improve the accuracy of ART self-report, the WIHS cohort employs medication photo-ID cards to prompt recall, and offers participants the option of bringing their medications to study visits to assist in identification. A clinical examination and blood draw for laboratory testing is also performed at each study visit. The WIHS does not provide clinical care; therefore ART is prescribed by the participant's treating clinician.

The MACS is the largest prospective, observational cohort study of the natural and treated history of HIV among men who have sex with men in the US. Participants were recruited from 4 centers located in the Baltimore, MD/Washington D.C., Chicago, IL, Pittsburgh, PA, and Los Angeles, CA, during three recruitment waves in 1984–1985 (n=4,954 men), 1987–1991 (n=668 men), and 2001–2003 (n=1,351 men). Similar to the WIHS, participants undergo semi-annual study visits with an extensive interview, clinical examination and

blood draw; the MACS does not provide clinical care. The MACS cohort has also been described elsewhere.(Chmiel et al., 1987; Dudley et al., 1995; Kaslow et al., 1987)

Demographic, laboratory, and antiretroviral treatment data collected from both cohorts were combined for this study. All HIV-infected WIHS and MACS participants who reported using ART between January 1, 2001 and December 31, 2007 were considered eligible. Study visits at which women were pregnant and using ART for prevention of mother to child transmission were excluded from the analysis.

Outcome of interest

The outcome measured for this study was whether the reported antiretroviral regimen was consistent or inconsistent with HIV treatment guideline recommendations in place at the time of study visit. ART combinations reported by participants at each study visit were analyzed. DHHS treatment guidelines issued between 2000 and 2007 were reviewed and regimens were date-matched to the guidelines to evaluate if the treatment was consistent with guidelines (Table 1). Visits where participants reported using combinations that were listed in the guidelines as “not recommended” or “generally not recommended” were classified as having guideline-inconsistent ART.

Exposure of interest and potential predictors

The exposure of interest is gender, which was categorized by participant self-report as male or female. Additional covariates of interest were identified based on important differences that exist between the male and female participants in the MACS and WIHS. Race was measured by self-report upon initial enrollment into the MACS and WIHS studies. At the visit in which ART was first reported, self-reported highest educational attainment, annual household income, employment status, drug and alcohol use in the last six months, health and prescription drug insurance, and the presence of depressive symptoms were measured. Health insurance status was classified as public (including Medicaid/Medi-CAL, Medicare, and Veteran's health insurance), private and none. Having prescription drug insurance was classified as reporting any prescription drug insurance (including AIDS Drug Assistance Program) versus none. A Center for Epidemiologic Studies Depression score (CES-D) of ≥ 16 was used to classify participants as having depressive symptoms. CD4 and HIV RNA were measured at, and 6-months prior to, ART initiation using standard techniques at laboratories which participate in National Institutes of Health/National Institute of Allergies and Infectious Diseases quality assurance programs. Having an AIDS-defining clinical condition was measured at, and the visit prior to, ART initiation, classified as self-reporting a clinical AIDS diagnosis (defined by the 1993 Centers for Disease Control and Prevention surveillance definition, excluding CD4 count < 200 cells/mm³).(CDC)

Statistical analyses

Statistical differences in the proportions and means of participant characteristics upon inclusion into our study were determined using the chi square (or Fisher's Exact) and Student's t test statistics, respectively. A secular trend in the proportion with guideline-inconsistent ART regimens was tested using the Cochran-Armitage test of trend for proportions. Crude (OR) and adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) were estimated using logistic regression models with generalized estimating equations (GEE) to account for within-individual correlations.(Spiegelman & Hertzmark, 2005; Zeger, Liang, & Albert, 1988; Zocchetti, Consonni, & Bertazzi, 1997) Data were initially stratified by gender to determine sex-specific covariates of guideline-inconsistent ART. Covariates with face validity or with statistically significant univariate associations were included in the models. Then, data from men and women were combined to estimate the association of gender on receipt of guideline inconsistent ART. The final model included covariates with

statistically significant, gender-specific univariate associations, as well as covariates with face validity. STATA version 10.0 (College Station, TX) was used for all analyses and a two-sided p-value of <0.05 guided interpretation.

Results

A total of 1672 WIHS women and 1265 MACS men reported using ART at 22,250 study visits occurring between January 1, 2001 and December 31, 2007. WIHS women were predominantly younger Black women, with lower educational attainment, lower household incomes, and greater use of public health medical payors as compared to MACS men (Table 2). MACS men had a higher mean CD4 count, a lower mean $\log_{10}$ HIV-1 RNA, and did not report a CDC-defined AIDS diagnosis as frequently as WIHS women, when they entered our study.

Guideline inconsistent ART was reported by 463 participants (16%) at n=922 study visits (4%) from 2001–07. Of the study visits where participants reported using guideline inconsistent ART many were subpotent regimens (e.g. mono/dual therapy; 67% WIHS; 59% MACS; 63% combined). Some participants reported toxic combinations (e.g. didanosine + stavudine; 17% WIHS; 28% MACS; 22% combined) at their visits. Fewer participants reported adversely interacting combinations (e.g. zidovudine + stavudine; 15% WIHS; 12% MACS; 14% combined) or combinations which were otherwise not recommended (e.g. enfuvirtide for treatment naïve patients; <1% for WIHS, MACS and combined) during their study visits. The most frequently reported guideline-inconsistent regimens included use of didanosine plus stavudine after November 2003 (21% combined), use of dual drug therapy between July 2003–October 2004 (20% combined), use of saquinavir as the sole PI after the year 2000 (14% combined), and ART monotherapy used during 2001–2006 (12% combined). Figure 1 illustrates the prevalence of guideline-inconsistent regimens by calendar year and cohort. The proportion of visits at which participants reported using guideline inconsistent ART remained stable over the study period, ranging from 3–8% (p for trend = 0.70). The prevalence of guideline-inconsistent ART peaked in 2004, likely due to the influx of four new antiretroviral agents in 2003, and two updates to the DHHS guidelines issued during 2004. There was no linear trend over time in the prevalence of guideline inconsistent ART for WIHS (p = 0.43) or MACS participants (p = 0.92).

Potential factors that may influence the receipt of guideline-inconsistent ART were examined by gender (Table 3). For WIHS women, having a higher HIV viral load at the previous study visit (OR=1.17, 95% CI 1.08, 1.27) was associated with a greater odds of reporting a guideline inconsistent regimen. Having a CD4 count ≥ 350 cells/mm³ measured at the prior study visit was associated with a 34% decrease in odds of reporting guideline-inconsistent ART (OR= 0.66, 95% CI 0.47, 0.94). After adjustment for age, race, insurance payor type, prescription drug coverage, prior visit CD4 count, and prior visit HIV viral load, only HIV viral load remained a significant predictor of a guideline-inconsistent regimen in WIHS women (aOR=1.16, 95% CI 1.05, 1.27).

For MACS men, higher HIV viral load at the prior study visit (OR=1.11, 95% CI 1.00, 1.23) was also associated with guideline inconsistent ART in univariate analyses (Table 3). A statistically significant association between having a higher HIV viral load and receipt of guideline-inconsistent ART remained (aOR=1.19, 95% CI 1.07, 1.34) after adjustment for age, race, insurance payor type, prescription drug coverage, and prior visit CD4 count.

In the analysis that included both men and women, gender was not associated with reporting guideline inconsistent ART in univariate or multivariate models (Table 4). Age greater than 50 years (OR=1.19, 95% CI 1.13, 3.32), moderate consumption of alcoholic beverages

(OR=1.35, 95% CI 1.05, 1.74), and higher HIV viral load at the prior study visit (OR=1.13, 95% CI 1.06, 1.21) were linked to guideline inconsistent ART. After adjustment for gender, race, insurance payor, prescription drug coverage, and prior visit CD4 count, age over 50 (aOR=2.22, 95% CI 1.14, 4.33) and HIV viral load (aOR=1.17, 95% CI 1.09, 1.26) retained a statistically significant association with reporting guideline-inconsistent ART.

Discussion

Our study found that use of guideline-inconsistent ART did not significantly differ by gender in two large cohorts of HIV-infected persons in the United States. Previous studies have found important gender-based differences in the receipt and quality of ART. Female sex has been associated with a lower likelihood of receiving any HAART (OR 0.68, 95% CI 0.60–0.76), early ART, and lower likelihood of starting a protease inhibitor based regimen. (McNaghten et al., 2003), (Andersen et al., 2000; Mocroft et al., 2000; Smith & Kirking, 1999) Our study used treatment guidelines, rather than a benchmark drug class, to classify appropriateness of regimens. Guidelines serve as a more specific quality marker in that they outline components of ART regimens which should be avoided for lack of potency as well as increased toxicity. Our study was also conducted in a more recent era of HAART where knowledge of HIV and its treatment is better disseminated amongst clinicians. Our study does not refute prior studies, but rather adds to their story: women may be less likely to receive ART because they enter into HIV care later or because they are less likely to seek HIV specialist care. (Andersen et al., 2000; Crystal, Sambamoorthi, & Merzel, 1995; Cunningham et al., 2000; Gardner et al., 2002; Smith & Kirking, 1999; Sohler, Li, & Cunningham, 2009). Yet, when women are in care and receiving ART, our study suggests that their treatment is as concordant with guidelines as it is for males. This finding is reassuring, but measures to promote equal ART must continue to be enforced. Participants in the WIHS are likely to have better access to care and ART compared to women in developing nations, therefore clinicians and administrators must still remain vigilant to reduce potential treatment disparities.

In the gender-specific and combined analyses, older age and increasing HIV viral load were associated with reporting a guideline inconsistent ART regimen. Older participants may be more treatment experienced and may require what would otherwise be suboptimal regimens; they may have reported their regimens inaccurately, or they may have been taking their ART in a manner that was different than was prescribed. Having a higher viral load at the prior study visit was also associated with a small, but statistically significant, increase in odds of reporting guideline-inconsistent ART. This association could be due to ART-experienced patients with high viral loads having limited choices and resulting in the use of more toxic combinations, or the use of low-potency or antagonistic ART continued from one study visit to the next.

A major limitation to our analysis is the difference between the MACS and WIHS cohorts with regards to other factors than gender, which could result in residual confounding and a masking of the association of gender and guideline-inconsistent ART use. These differences, however, reflect the differences in the HIV epidemic in the US. Adjustment for important potential confounders, including race, insurance type and prescription drug insurance resulted in no correlation between gender and the use of guideline-inconsistent ART. Further, these confounders were not correlated with guideline-inconsistent ART in univariate or multivariate analyses, suggesting they are not masking a gender association. The WIHS is reflective of the characteristics of the US HIV epidemic among women while the MACS is reflective of the US HIV epidemic among gay and bisexual men. It is unknown whether reports of guideline-inconsistent ART would differ between women and heterosexual men. Some studies have suggested that homosexual and heterosexual men may

differ in ART uptake, but differences in the classes of ART used by these groups is not well-described.(Easterbrook et al., 2008) Another potential limitation of our study is the reliance on self-reported measures of antiretroviral regimens. Recall bias may have been minimized by the use of highly-trained interviewers, picture-photo medication cards, and pill review (when participants bring their medications), however it cannot be eliminated completely. The WIHS and MACS are observational studies which do not currently collect information on the clinicians who care for study participants; provider characteristics such as experience in treating HIV infected individuals may be closely linked to the prescribing patterns seen in our study.

Lastly, our analyses may underestimate the frequency of use of guideline-inconsistent regimens. Men and women participating in the MACS and WIHS cohort studies may have been more likely to receive ART that is guideline consistent compared to HIV patients in general because they live in urban areas with a higher prevalence of HIV infection and greater access to centers of expertise. Though the MACS and WIHS studies do not provide clinical care, the participants are in contact with investigators based at sites that do care for large numbers of HIV-infected patients. Participants may receive information from their cohort studies that may assist them in getting optimal HIV and antiretroviral care.

Conclusion

In the modern era of HAART, use of guideline inconsistent ART did not differ by gender. Age and higher viral load were associated with receipt of guideline inconsistent ART. Although the prevalence of guideline inconsistent therapy remained low over the study timeframe, it could be a significant contributor to the occurrence of regimen failure and/or adverse effects. Thus, monitoring the use of ART amongst patient subgroups may have substantial benefits. The continual introduction of new antiretroviral agents and increasing complexity of combinations calls for continued efforts to promote optimal ART for all HIV-infected patients.

Acknowledgments

Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS) Collaborative Study Group and the Multicenter AIDS Cohort Study (MACS). WIHS has centers (Principal Investigators) at New York City/ Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington DC Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); Data Coordinating Center (Stephen Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases (U01-AI-35004, U01-AI-31834, U01-AI-34994, U01-AI-34989, U01-AI-34993, and U01-AI-42590) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (U01-HD-32632) with co-funding from the National Cancer Institute, the National Institute on Drug Abuse, National Institute on Deafness and Other Communication Disorders, and the National Center for Research Resources (UCSFCTSI Grant Number UL1 RR024131). The MACS has centers (Principal Investigators) at The Johns Hopkins University Bloomberg School of Public Health (Joseph B. Margolick, Lisa Jacobson), Howard Brown Health Center and Northwestern University Medical School (John Phair), University of California, Los Angeles (Roger Detels), and University of Pittsburgh (Charles Rinaldo). The MACS is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute and the National Heart, Lung and Blood Institute. U01-AI-35042, 5-MO1-RR-00722 (GCRC), U01-AI-35043, U01-AI-37984, U01-AI-35039, U01-AI-35040, U01-AI-37613, U01-AI-35041. The MACS website is located at <http://www.statepi.jhsph.edu/mac/mac.html>. Dr. Cocohoba's research is funded by the Building Interdisciplinary Research Careers in Women's Health Program (K12HD052163) and the National Institutes of Mental Health (K23MH087218). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

References

Andersen R, Bozzette S, Shapiro M, St Clair P, Morton S, Crystal S, et al. Access of vulnerable groups to antiretroviral therapy among persons in care for HIV disease in the United States. HCSUS

- Consortium. HIV Cost and Services Utilization Study. *Health Serv Res.* 2000; 35(2):389–416. [PubMed: 10857469]
- Bacon MC, von Wyl V, Alden C, Sharp G, Robison E, Hessel N, et al. The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. *Clin Diagn Lab Immunol.* 2005; 12(9):1013–1019. [PubMed: 16148165]
- Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, Miotti P, et al. The Women's Interagency HIV Study. WIHS Collaborative Study Group. *Epidemiology.* 1998; 9(2):117–125. [PubMed: 9504278]
- CDC 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults. *Journal.* December 18, 1993 (41) RR-17.
- Chmiel JS, Detels R, Kaslow RA, Van Raden M, Kingsley LA, Brookmeyer R. Factors associated with prevalent human immunodeficiency virus (HIV) infection in the Multicenter AIDS Cohort Study. *Am J Epidemiol.* 1987; 126(4):568–577. [PubMed: 3651095]
- Cocohoba J, Wang QJ, Cox C, Gange SJ, Cohen M, Glesby M, et al. Consistency of initial antiretroviral therapy with HIV treatment guidelines in a US cohort of HIV-infected women. *J Acquir Immune Defic Syndr.* 2008; 47(3):377–383. [PubMed: 18176324]
- Crystal S, Sambamoorthi U, Merzel C. The diffusion of innovation in AIDS treatment: zidovudine use in two New Jersey cohorts. *Health Serv Res.* 1995; 30(4):593–614. [PubMed: 7591783]
- Cunningham WE, Markson LE, Andersen RM, Crystal SH, Fleishman JA, Golin C, et al. Prevalence and predictors of highly active antiretroviral therapy use in patients with HIV infection in the United States. HCSUS Consortium. HIV Cost and Services Utilization. *J Acquir Immune Defic Syndr.* 2000; 25(2):115–123. [PubMed: 11103041]
- Dudley J, Jin S, Hoover D, Metz S, Thackeray R, Chmiel J. The Multicenter AIDS Cohort Study: retention after 9 1/2 years. *Am J Epidemiol.* 1995; 142(3):323–330. [PubMed: 7631636]
- Easterbrook PJ, Phillips AN, Hill T, Matthias R, Fisher M, Gazzard B, et al. Patterns and predictors of the use of different antiretroviral drug regimens at treatment initiation in the UK. *HIV Med.* 2008; 9(1):47–56. [PubMed: 18199172]
- Eisenman D, Bogart LM, Bird CE, Collins RL, Golinelli D, Fremont A, et al. Differential diffusion of HIV technologies by gender: the case of highly active antiretroviral therapy. *AIDS Patient Care STDS.* 2007; 21(6):390–399. [PubMed: 17594248]
- Gardner LI, Holmberg SD, Moore J, Arnsten JH, Mayer KH, Rompalo A, et al. Use of highly active antiretroviral therapy in HIV-infected women: impact of HIV specialist care. *J Acquir Immune Defic Syndr.* 2002; 29(1):69–75. [PubMed: 11782593]
- Gebo KA, Fleishman JA, Conviser R, Reilly ED, Korthuis PT, Moore RD, et al. Racial and gender disparities in receipt of highly active antiretroviral therapy persist in a multistate sample of HIV patients in 2001. *J Acquir Immune Defic Syndr.* 2005; 38(1):96–103. [PubMed: 15608532]
- Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009 Retrieved January 30, 2010, 2009, from <http://www.aidsinfo.nih.gov>
- Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol.* 1987; 126(2):310–318. [PubMed: 3300281]
- King WD, Minor P, Ramirez Kitchen C, Ore LE, Shoptaw S, Victorianne GD, et al. Racial, gender and geographic disparities of antiretroviral treatment among US Medicaid enrollees in 1998. *J Epidemiol Community Health.* 2008; 62(9):798–803. [PubMed: 18701730]
- McNaghten AD, Hanson DL, Dworkin MS, Jones JL. Differences in prescription of antiretroviral therapy in a large cohort of HIV-infected patients. *J Acquir Immune Defic Syndr.* 2003; 32(5):499–505. [PubMed: 12679701]
- Mocroft A, Gill MJ, Davidson W, Phillips AN. Are there gender differences in starting protease inhibitors, HAART, and disease progression despite equal access to care? *J Acquir Immune Defic Syndr.* 2000; 24(5):475–482. [PubMed: 11035619]
- Smith SR, Kirking DM. Access and use of medications in HIV disease. *Health Serv Res.* 1999; 34(1 Pt 1):123–144. [PubMed: 10201855]

- Sohler NL, Li X, Cunningham CO. Gender disparities in HIV health care utilization among the severely disadvantaged: can we determine the reasons? *AIDS Patient Care STDS*. 2009; 23(9): 775–783. [PubMed: 19663745]
- Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol*. 2005; 162(3):199–200. [PubMed: 15987728]
- Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics*. 1988; 44(4):1049–1060. [PubMed: 3233245]
- Zocchetti C, Consonni D, Bertazzi PA. Relationship between prevalence rate ratios and odds ratios in cross-sectional studies. *Int J Epidemiol*. 1997; 26(1):220–223. [PubMed: 9126523]

Figure 1.
Prevalence of study visits where participants reported using guideline inconsistent ART regimens, by gender and calendar year

Table 1

Antiretroviral combinations not recommended for use by the Department of Health and Human Services (DHHS) HIV Treatment Guidelines spanning January 2001– December 2007

Dates	Not Generally Recommended or Not Recommended
1/28/00 – 7/13/03 ^{a,b}	<p>Zidovudine + didanosine</p> <p>Stavudine + didanosine</p> <p>Zidovudine + zalcitabine</p> <p>Zidovudine + lamivudine</p> <p>Stavudine + lamivudine</p> <p>All monotherapies</p> <p>Stavudine + zidovudine</p> <p>Zalcitabine + didanosine</p> <p>Zalcitabine + stavudine</p> <p>Zalcitabine + lamivudine saquinavir hard-gel capsules + 2NRTIs^c didanosine + lamivudine as 2 NRTI combination</p> <p><i>Addition:</i> saquinavir hard-gel capsules as sole protease inhibitor</p>
7/14/03 – 11/9/03	<p><i>Additions:</i></p> <p>All 2-agent drug combinations</p> <p>Stavudine + didanosine use during pregnancy</p> <p>Efavirenz use during pregnancy</p> <p>Amprenavir oral solution use in pregnancy, children < 4 years old, renal/hepatic failure or by those taking metronidazole or disulfiram</p> <p>Hydroxyurea</p> <p><i>Deletion:</i> zalcitabine + lamivudine removed from list</p>
11/10/03 – 10/28/04 ^a	<p><i>Additions:</i></p> <p>Abacavir + tenofovir + lamivudine as a 3 NRTI regimen</p> <p>Tenofovir + didanosine + lamivudine as a 3 NRTI regimen</p> <p>Atazanavir + indinavir</p> <p>Emtricitabine + lamivudine</p> <p><i>Changes:</i> stavudine + didanosine not recommended for use in all patients</p>
10/29/04 – 4/6/05	<p><i>Additions:</i></p> <p>For initial therapy: amprenavir, delavirdine, enfuvirtide, indinavir or ritonavir or saquinavir SGC as the sole protease inhibitor, and zalcitabine + zidovudine</p> <p>Fosamprenavir + amprenavir</p> <p>Amprenavir oral solution + ritonavir oral solution</p> <p>Lamivudine + zalcitabine (returns to list)</p> <p><i>Changes:</i> efavirenz restriction changed to 1st trimester pregnancy and/or all women of child-bearing potential</p>
4/7/05 – 10/5/05	<p><i>Additions:</i></p> <p>For initial therapy: nevirapine at CD4+ cell counts > 250 for women or > 400 for men</p>
10/6/05 – 10/9/06 ^a	<p><i>Additions:</i></p> <p>For initial therapy: tipranavir, didanosine + tenofovir + NNRTI^d</p>

Dates	Not Generally Recommended or Not Recommended
10/10/06 – 11/31/07	<p><i>Additions:</i></p> <p>For initial therapy: darunavir, didanosine + tenofovir as the NRTI backbone, indinavir + ritonavir</p> <p>NRTI or NNRTI monotherapy</p> <p>3 NRTI therapy except for zidovudine + abacavir + lamivudine or Zidovudine + tenofovir+ lamivudine</p> <p><i>Deletions:</i></p> <p>Didanosine + tenofovir + NNRTI for initial therapy</p> <p>Amprenavir for initial therapy</p> <p>Didanosine + tenofovir + lamivudine</p> <p>Abacavir + tenofovir + lamivudine</p> <p>Antiretroviral monotherapy</p>
12/1/07 – 1/28/08	<p><i>Deletions:</i></p> <p>Zalcitabine + didanosine</p> <p>Zalcitabine + stavudine</p> <p>Zalcitabine + lamivudine</p> <p>Amprenavir + fosamprenavir</p> <p>Zidovudine + zalcitabine (dual therapy) for initial therapy</p>

^aThese dates include more than 1 iteration of the DHHS guidelines if the subsequent guideline(s) had no changes

^bNot generally recommended category no longer included in the DHHS guidelines. Regimen components classified under the “no recommendation category (insufficient data)” were not applied to this analysis.

^cNRTI = nucleoside reverse transcriptase inhibitor,

^dNNRTI = non-nucleoside reverse transcriptase inhibitor

Table 2

Baseline characteristics of participants reporting ART use, the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS), 2001–2007

Characteristic ^a	WIHS women (N=1841)	MACS men (N=1364)	p-value ^b
Age, mean (SD)	40 (8.6)	44 (8.6)	<0.0001
Race, n (%)			<0.001
White	424 (25)	816 (65)	
Black	938 (56)	347 (27)	
Other	310 (19)	102 (8)	
High School Diploma, n (%)	1035 (62)	1167(92)	<0.001
Annual household income >\$30,000, n (%)	269 (16)	523 (41)	<0.001
Employed, n (%)	549 (33)	667 (53)	<0.001
Health insurance, n (%)			<0.001
Private	419 (25)	783 (62)	
Public ^c	1013 (61)	273 (22)	
None	228 (14)	87 (7)	
Prescription drug insurance, n (%)	1248 (75)	1065 (84)	<0.001
Center for Epidemiologic Studies Depression Scale score > 15	1027 (61)	564 (45)	<0.001
Drug use in the last 6 months, n (%) ^d	75 (4)	269 (21)	<0.001
Alcohol use in the last 6 months, n (%)			<0.001
0 drinks/week	994 (59)	475 (38)	
< 3 drinks/week	450 (27)	322 (25)	
3–13 drinks/week	168 (10)	293 (23)	
>13 drinks/week	44 (3)	59 (5)	
Diagnosis of AIDS, n (%)	637 (38)	192 (15)	<0.001
Baseline CD4+ cell count (cells/mm3), mean (SD)			<0.001
≤ 200 cells/mm3	304 (18)	119 (9)	
201–349 cells/mm3	382 (23)	194 (15)	
≥ 350 cells/mm3	984 (59)	950 (75)	
Baseline HIV viral load (log copies/mL), mean (SD)	2.7 (1.1)	2.3 (1.1)	<0.0001

^aPercentages may not add up to 100% due to missing data

^bChi-Square used for categorical variables & Student's T-Test used for continuous variables.

^cPublic health insurance includes Medicaid/Medi-CAL, Medicare, and Veteran's health insurance.

^dDrug use includes injecting or non-injection use of any of the following: marijuana, crack, cocaine, heroin, amphetamines, methamphetamines, non-prescription methadone or narcotics.

Table 3

Univariate and adjusted odds of reporting a guideline inconsistent antiretroviral regimen, by gender, the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS), 2001–2007

	WIHS women		MACS men	
	Univariate OR (95% CI)	Adjusted ^a OR (95% CI)	Univariate OR (95% CI)	Adjusted ^a OR (95% CI)
Age (years)				
<30	1.00	1.00	1.00	1.00
30–39	1.17 (0.65–2.12)	1.15 (0.55–2.40)	0.68 (0.21–2.25)	0.64 (0.16–2.48)
40–49	1.29 (0.72–2.33)	1.35 (0.65–2.82)	1.50 (0.49–4.58)	1.37 (0.37–5.07)
>50	1.79 (0.95–3.38)	2.06 (0.95–4.46)	2.04 (0.67–6.24)	2.19 (0.60–8.04)
Race, n (%)				
White	1.00	1.00	1.00	1.00
Black	1.22 (0.81–1.85)	1.08 (0.70–1.66)	0.91 (0.60–1.36)	1.05 (0.63–1.75)
Other	1.37 (0.81–2.30)	1.24 (0.73–2.12)	0.65 (0.32–1.29)	1.13 (0.46–2.79)
High school diploma, n (%)	0.81 (0.59–1.12)	---	1.36 (0.73–2.56)	---
Annual household income >\$30,000, n (%)	0.81 (0.56–1.17)	---	0.94 (0.69–1.28)	---
Employed, n (%)	0.85 (0.67–1.07)	---	1.11 (0.81–1.51)	---
Health insurance, n (%)				
Private	1.00	1.00	1.00	1.00
Public ^b	1.25 (0.94–1.65)	1.09 (0.80–1.49)	1.10 (0.76–1.59)	1.15 (0.74–1.80)
None	0.99 (0.70–1.40)	0.91 (0.53–1.57)	0.56 (0.26–1.21)	0.75 (0.31–1.80)
Prescription drug insurance, n (%)	1.26 (0.92–1.71)	1.11 (0.76–1.61)	0.82 (0.51–1.32)	0.67 (0.40–1.12)
Center for Epidemiologic Studies Depression score > 15	0.86 (0.70–1.06)	---	1.24 (0.98–1.58)	---
Drug use in the last 6 months, n (%) ^c	0.94 (0.51–1.71)	---	0.87 (0.64–1.19)	---
Alcohol use in the last 6 months		---		
0 drinks/week	1.00	---	1.00	1.00
< 3 drinks/week	1.15 (0.92–1.43)	---	1.02 (0.76–1.37)	---
3–13 drinks/week	1.16 (0.76–1.76)	---	1.46 (1.04–2.06)	---
>13 drinks/week	0.79 (0.30–2.08)	---	1.06 (0.54–2.08)	---
Having AIDS at the visit the regimen was reported	1.22 (0.92–1.61)	---	1.04 (0.71–1.52)	---
At the prior visit				
CD4+ T-lymphocyte count ≤ 200 cells/mm ³	1.00	1.00	1.00	1.00
CD4+ T-lymphocyte count 201–349 cells/mm ³	0.98 (0.69–1.40)	1.13 (0.77–1.66)	0.84 (0.43–1.66)	1.01 (0.51–1.99)
CD4+ T-lymphocyte count ≥ 350 cells/mm ³	0.66 (0.47–0.94)	0.85 (0.58–1.27)	1.15 (0.66–2.02)	1.42 (0.75–2.67)
HIV -1 RNA (log10 copies/mL)	1.17 (1.08–1.27)	1.16 (1.05–1.27)	1.11 (1.00–1.23)	1.19 (1.07–1.34)
Visit year	1.02 (0.96–1.08)	---	1.02 (0.95–1.09)	---

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval

^a Adjusted for race, age, prescription drug coverage, insurance type, prior visit CD4+ cell count category and log10 HIV viral load.

^b Public health insurance includes Medicaid/Medi-CAL, Medicare, and Veteran's health insurance.

^c Drug use includes injecting or non-injection use of any of the following: marijuana, crack, cocaine, heroin, amphetamines, methamphetamines, non-prescription methadone or narcotics.

Table 4

Factors associated with reporting guideline inconsistent antiretroviral therapy, the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS), 2001–2007

	Univariate OR (95% CI)	Adjusted ^a OR (95% CI)
Sex	1.14 (0.90–1.43)	1.19 (0.87–1.63)
Age (years)		
<30	1.00	1.00
30–39	1.03 (0.60–1.75)	1.04 (0.54–2.01)
40–49	1.39 (0.83–2.35)	1.42 (0.74–2.71)
>50	1.93 (1.13–3.32)	2.22 (1.14–4.33)
Race, n (%)		
White	1.00	1.00
Black	0.97 (0.76–1.24)	1.04 (0.75–1.42)
Other	0.98 (0.68–1.43)	1.15 (0.74–1.78)
High school diploma, n (%)	0.96 (0.73–1.26)	---
Annual household income >\$30,000, n (%)	0.91 (0.73–1.14)	---
Employed, n (%)	0.96 (0.81–1.15)	---
Health insurance, n (%)		
Private	1.00	1.00
Public ^b	1.11 (0.89–1.37)	1.10 (0.85–1.42)
None	0.81 (0.59–1.10)	0.82 (0.52–1.30)
Prescription drug insurance, n (%)	1.15 (0.89–1.49)	0.99 (0.73–1.34)
Center for Epidemiologic Studies Depression score > 15	0.99 (0.85–1.17)	---
Drug use ^c in the last 6 months, n (%)	0.91 (0.69–1.20)	---
Alcohol use in the last 6 months		
0 drinks/week	1.00	---
< 3 drinks/week	1.09 (0.92–1.30)	---
3–13 drinks/week	1.35 (1.05–1.74)	---
>13 drinks/week	0.95 (0.55–1.64)	---
Having AIDS at the visit the regimen was reported	1.11 (0.89–1.38)	---
At the prior visit		
CD4+ T-lymphocyte count ≤ 200 cells/mm ³	1.00	1.00
CD4+ T-lymphocyte count 201–349 cells/mm ³	0.94 (0.69–1.29)	1.10 (0.79–1.53)
CD4+ T-lymphocyte count ≥ 350 cells/mm ³	0.83 (0.63–1.09)	1.02 (0.74–1.42)
HIV -1 RNA (log10 copies/mL)	1.13 (1.06–1.21)	1.17 (1.09–1.26)
Visit year	1.02 (0.97–1.06)	---

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval

^aFor the adjusted model, covariates included gender, age, race, insurance type, prescription drug coverage, prior visit CD4+ T-lymphocyte count category and log10 HIV viral load.

^bPublic health insurance includes Medicaid/Medi-CAL, Medicare, and Veteran's health insurance.

^cDrug use includes injecting or non-injection use of any of the following: marijuana, crack, cocaine, heroin, amphetamines, methamphetamines, non-prescription methadone or narcotics.