Age, adherence and injection drug use predict virological suppression among men and women enrolled in a population-based antiretroviral drug treatment programme

Jacqueline M O'Connell[1], Paula Braitstein[1], Robert S Hogg[1,4], Benita Yip[1], Kevin JP Craib[1], Michael V O'Shaughnessy[1,2], Julio SG Montaner[1,3] and David R Burdge[3,5]*

[1]BC Centre for Excellence in HIV/AIDS; Departments of [2]Pathology and Laboratory Medicine; [3]Medicine; and [4]Health Care and Epidemiology; Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[5]Oak Tree Clinic, Vancouver, British Columbia, Canada

*Corresponding author: Tel: +1 604 806 8516; Fax: +1 604 806 9044; E-mail: bobhogg@hivnet.ubc.ca

Objectives: To characterize 1-year virological response to antiretroviral therapy and its determinants by sex.
Methods: This is a population-based analysis of antiretroviral therapy naive HIV-positive adult men and women. Factors associated with sex and with plasma HIV RNA viral load suppression to below 500 copies/ml were examined using non-parametric tests and logistic regression analyses.
Results: A total of 739 subjects (92 women and 647 men) were eligible. Female participants were younger (34 vs 37 years; *P*<0.001), less likely to have AIDS (6.5 vs 14.4%; *P*=0.039), more frequently injection drug users (44.6 vs 25.2%; *P*=0.001) and were less likely to be adherent to therapy (34.8 vs 62.9%; *P*<0.001) than male participants. There was no difference in baseline median CD4 count (*P*=0.424) or HIV RNA levels (*P*=0.140), physician experience (*P*=0.057), or with respect to antiretroviral regimens containing protease inhibitors or non-nucleoside reverse transcriptase inhibitors (*P*=0.911). With treatment, 46.7% (43/92) of women and 64.8% (419/647) of men (*P*=0.001) suppressed HIV RNA viral load to below 500 copies/ml at 1 year. In a multivariate analysis, the association of sex with HIV RNA response to antiretroviral therapy fell from statistical significance (odds ratio 1.18; 95% CI: 0.72–1.95) after adjusting for adherence, injection drug use and age.
Conclusion: Our data indicate that in this population-based setting, sex differences in 1-year virological response to antiretroviral therapy are explained by age, adherence and injection drug use.

Introduction

Triple-drug antiretroviral therapy is currently recommended as the standard first-line therapy for patients infected with HIV [1]. It has been shown to increase short-term survival, decrease morbidity, improve CD4 cell counts and decrease plasma viral load [1–3]. Thus far, clinical guidelines for antiretroviral therapy have been established from studies performed predominantly among men, but are applied uniformly to women and men [1,4]. With the increase in the incidence of HIV/AIDS in women in the last decade [5], potential sex differences in HIV infection have become important considerations in the assessment and treatment of men and women with HIV/AIDS. Differences by sex in baseline plasma HIV-1 RNA levels [6–12], CD4 lymphocyte (CD4) counts [10,13,14], and progression to AIDS and death [15] have been reported. However, the mechanisms for these differences remain largely unidentified and are still subject to debate as other studies have failed to confirm these observations [16–20].

Inasmuch as it is important to study sex differences in disease progression, because treatment guidelines are based on disease markers and do not include a stratification by sex, it is equally important to explore sex differences in response to highly active antiretroviral therapy (HAART). In spite of several plausible postulates, there has been little conclusive evidence to indicate that there are clinically significant sex differences in viral load response to antiretroviral therapy [21–25]. Information on relative viral load responses to therapy between the sexes may provide relevant information of assistance in determining how best to achieve optimal treatment response in both men and women. We conducted the present analyses to characterize and explore the determinants of plasma HIV RNA suppression to below 500 copies/ml in women

and men in British Columbia who first started triple-drug antiretroviral therapy between 1996 and 1998. This is among the first population-based studies investigating sex differences in response to antiretroviral therapy.

Methods

HIV/AIDS Drug Treatment Program

Since 1992, the HIV/AIDS Drug Treatment Program at the British Columbia (BC) Centre for Excellence in HIV/AIDS has distributed antiretroviral therapy at no cost to eligible HIV-infected residents of BC. Medication is dispensed on the basis of protocols established by the Therapeutic Guidelines Committee [26]. These guidelines are reviewed annually and have remained consistent with those published by the International AIDS society USA [1,27,28].

Data collection

HIV-1 antibody-positive participants are recruited into the provincial HIV/AIDS Drug Treatment Program upon completion of a physician administered drug request enrolment form. Upon enrolment, each participant is asked to complete a programme consent form and survey, and the physician is asked to complete a clinical staging form. The clinical staging form records participant-specific information on HIV/AIDS-related conditions according to the World Health Organization's clinical staging system [29]. Participant surveys and clinical staging forms are re-administered annually.

Our retrospective analysis was restricted to HIV-positive men and women who first started triple-drug antiretroviral therapy between August 1996 and September 1998. Participants were followed until January 31 2001. In June 1996 the BC Centre for Excellence in HIV/AIDS adopted plasma viral load-driven antiretroviral therapy guidelines, consistent with those put forward by the International AIDS Society – USA [30]. In brief, antiretroviral therapy naive individuals with plasma viral load >100 000 copies/ml were offered triple-drug regimens (that is, two nucleosides plus a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor), while those with plasma viral loads from 5000 to 100 000 copies/ml were offered dual nucleoside therapy. In July of 1997, the guidelines were revised to recommend triple combination therapy for all antiretroviral-naive individuals with plasma viral loads ≥5000 copies/ml or a CD4 cell count below 500 cells/mm^3 [1,27,28]. Later on, the guidelines were revised again, and combination therapy is now recommended for patients with CD4 <350 cells/mm^3.

Participants were included in the study if they were 18 years of age or older, had baseline plasma HIV RNA levels above 500 copies/ml, and had at least 16 months of follow-up after initiation of antiretroviral therapy. Baseline values refer to the last measures taken prior to the first start date of antiretroviral therapy. Plasma viral load was measured using Amplicor HIV-1 Monitor™ (Roche Diagnostic Systems, Branchburg, NJ, USA). For this study, plasma viral load of 500 copies/ml was chosen as the threshold measure for suppression and non-suppression of viral load in keeping with testing standards for the period beginning in August 1996, and for consistency through the study period. Sixteen months of follow-up was selected *a priori*, as it provides a conservative time window for virological suppression after 1 year from treatment start date.

Patient information was obtained through self-administered voluntary questionnaire. For this study, adherence was defined as the number of months of medication dispensed divided by the number of months of follow-up in the first year, expressed as percentages. Ninety-five percent adherence to therapy has been associated with high treatment success as measured by viral load suppression [31, 32]. Thus, adherent participants in this study are considered to be those who have been 95% adherent to treatment. Physician experience was estimated from the cumulative number of treated HIV-positive patients the physician had followed at the time when the participant first started antiretroviral therapy [33].

Outcome measures

The primary outcome measure in our analysis was plasma HIV RNA viral load suppression to less than 500 copies/ml in the last available viral load measurement, at least 1 year after the start of antiretroviral therapy.

Statistical analysis

We followed an intent-to-treat principle – subjects were retained in their initial treatment groups irrespective of therapy switching – because it provided us with the most conservative estimate of true treatment effect. Statistical comparisons of baseline data stratified by sex and by viral load response were conducted using distribution-free methods. Categorical variables and continuous variables were compared with Pearson's χ^2 statistics and Wilcoxon rank sum non-parametric tests, respectively.

Logistic regression analyses were used to determine if sex, age, AIDS, baseline HIV RNA levels, baseline CD4, injection drug use, adherence and physician experience were associated with HIV RNA suppression to less than 500 copies/ml after initiation of triple-drug antiretroviral therapy. To assess independent predictors of HIV RNA viral load suppression, variables significant in univariate analyses (P<0.05) were considered in

multivariate logistic regression models. As have others [34], we evaluated suppression levels by fitting logistic models since we sought to evaluate factors associated with ever achieving plasma HIV RNA suppression. This approach was selected since we assumed that ever achieving HIV RNA suppression would be more clinically relevant than the time to HIV RNA suppression [35]. All reported *P*-values are two-sided.

Results

Of 856 Drug Treatment Program participants, 117 (13.7%) were excluded from the study. Those who were excluded from this study were significantly more likely to be women. Our analysis was based on 739 participants who started naive on triple combination antiretroviral therapy upon enrolment into the HIV/AIDS Drug Treatment Program between August 1996 and September 1998. In total, there were 92 women (12%) and 647 men (88%) in this study group. Median follow-up time for participants in this study was 28 (IQR: 22–33) months.

As shown in Table 1, female participants were younger (median 34 vs 37 years; $P<0.001$), less likely to have AIDS (6.5 vs 14.4%; $P=0.039$) and more likely to be injection drug users (44.6 vs 25.2%; $P=0.001$) than male participants. There was no sex difference with respect to median baseline CD4 count ($P=0.424$), median baseline HIV RNA levels ($P=0.140$) or physician experience ($P=0.057$). Female participants were less likely to be 95% adherent to their antiretroviral treatment regimen (34.8 vs 62.9%; $P=0.001$) than male participants. There was no statistically significant sex difference with respect to antiretroviral regimens containing protease inhibitors or non-nucleoside reverse transcriptase inhibitors ($P=0.911$).

Table 2 shows that men were significantly more likely to achieve HIV RNA levels below 500 copies/ml than women. Specifically, 43 out of 92 (46.7%) women and 419 out of 647 (64.8%) men ($P=0.001$) achieved an HIV RNA viral load response. Participants who achieved HIV RNA suppression to below 500 copies/ml were more likely to be older (38 vs 35 years; $P<0.001$) and to have a lower median baseline CD4 lymphocyte count (270 vs 340 cells/mm^3; $P=0.003$). Those with a diagnosis of AIDS ($P=0.003$) and those who were 95% adherent to antiretroviral treatment ($P=0.001$) were more likely to suppress viral load. Injection drug users were less likely to achieve viral load suppression than those who did not use injection drugs (50.0 vs 67.3%; $P=0.001$). Baseline plasma viral load was not significantly different in those who did and did not achieve an HIV RNA response to below 500 copies/ml ($P=0.650$).

Table 1. Association between sex and clinical characteristics of 739 HIV-positive participants first prescribed any triple combination antiretroviral therapy between August 1 1996 and September 30 1998 (column percentages shown)

Baseline variable	Female (*n*=92)	Male (*n*=647)	*P*-value
Age (years)			
Median	34	37	<0.001
(interquartile range)	(29–40)	(32–44)	
Plasma HIV RNA (copies/ml)			
Median	105000	140000	0.140
(interquartile range)	(35000–340000)	(55000–310000)	
CD4 (cells/mm^3)			
Median	310	300	0.424
(interquartile range)	(160–440)	(130–450)	
AIDS diagnosis			
No	86 (93.5%)	554 (85.6%)	0.039
Yes	6 (6.5%)	93 (14.4%)	
Injection drug use			
Yes	41 (44.6%)	163 (25.2%)	0.001
No	51 (55.4%)	484 (74.8%)	
95% adherence			
Yes	32 (34.8%)	407 (62.9%)	0.001
No	60 (65.2%)	240 (37.1%)	
Physician experience			
Median	48	43	0.057
(interquartile range)	(3–92)	(5–137)	
HAART regimen			
PI	81 (88.0%)	567 (87.6%)	0.911
NNRTI	11 (12.0%)	80 (12.4%)	

As shown in Table 3, there was no statistically significant sex difference in HIV RNA suppression to below 500 copies/ml after adjusting for adherence, injection drug use and age (adjusted odds ratio 1.18; 95% CI: 0.72–1.95). In confirmatory analyses, we found that no combination of other potential confounders (baseline plasma viral load, baseline CD4 counts, physician experience, AIDS diagnosis, non-nucleoside reverse transcriptase inhibitor and protease inhibitor regimens) significantly changed these estimates, and these estimates were not significantly affected when adherence was considered as a continuous variable (data not shown). Model diagnostics did not detect any significant interactions. Also, since treatment guidelines changed during the study period, we evaluated whether calendar period might confound any sex effect. In both univariate and multivariate analyses, calendar period (before versus after July 1997) was not statistically significant (data not shown). Results were similar, where gender was significant univariately but fell from

Table 2. Association between HIV RNA plasma viral load response below 500 copies/ml and clinical characteristics of 739 HIV-positive participants

Baseline variable	HIV RNA response		*P*-value
	Not suppressed: ≥500 copies/ml (*n*=277)	Suppressed: <500 copies/ml (*n*=462)	
Sex			
Female	49 (53.3%)	43 (46.7%)	0.001
Male	228 (35.2%)	419 (64.8%)	
Age	35.3 (31.6-42.0)	37.7 (32.9-44.0)	<0.001
Plasma HIV RNA (copies/ml)			
Median (interquartile range)	130000 (48000–340000)	130000 (50000–300000)	0.650
CD4 (cells/mm^3)			
Median (interquartile range)	340 (180–480)	270 (120–430)	0.003
AIDS			
Yes	24 (24.2%)	75 (75.8%)	0.003
No	253 (39.5%)	387 (60.5%)	
Injection drug use			
Total number of IDU	102 (50.0%)	102 (50.0%)	0.001
Total number of non-IDU	175 (32.7%)	360 (67.3%)	
95% adherence			
Total number who were ≥95% adherent	90 (20.5%)	349 (79.5%)	0.001
Total number who were <95% adherent	187 (62.3%)	113 (37.7%)	

(row percentages presented).

significance in the multivariate model, when we evaluated the time to suppression using cox regression analyses.

Table 4 shows results of a sub-analysis focusing on treatment adherence. In our cohort, participants who were more likely to be adherent to treatment were male and were slightly older. Among the suppressed individuals, there were a higher proportion of men who were adherent than women (78 vs 56%). Similarly, among the non-suppressed participants, 36% of the men were adherent while only 16% of the women were adherent. The same pattern is seen with injection drug users, with a higher proportion of men (49%) having 95% adherence than women (27%). Likewise, among the non-injection drug users, a higher proportion of males were 95% adherent than females (68 vs 41%).

Discussion

Our data demonstrate that women prescribed triple combination antiretroviral therapy in British Columbia, Canada, did not achieve as full viral load suppression as men after at least 1 year of follow-up. However, our analyses indicate that sex differences in virological suppression after 1 year are explained by an imbalance of known predictors (age, injection drug use and adherence) between men and women.

Sex differences in biological markers of HIV disease have been reported [6–12,36], however, the clinical significance of these findings is still unclear [9,16]. Further, several prospective studies have found no difference according to sex in survival and progression to AIDS, in spite of some initial viral load differences in men and women [15,17,37]. Overall, whether a clinically important sex difference in viral load or time to progression to AIDS exists is still unclear. However, what of sex differences in response to treatment once started?

Antiretroviral therapy has been shown to benefit men and women [38], and at present, treatment guidelines recommend antiretroviral treatment based on clinical, virological and immunological status, but not sex [1]. Many biological reasons have been postulated for why women might have a different response to antiretroviral treatment than men. Women and men may show differential drug absorption [39], disparities in median body weight [40] and hormonal differences [4,41], all of which theoretically may result in differential response to treatment. Further, recent work suggests that a sex difference in virus–host interactions not explained by clinical disease status may exist [6,42,43]. In spite of many plausible postulates, there has been little conclusive evidence to indicate that there are clinically significant sex differences in virological

Table 3. Multivariate logistic regression models of clinical factors associated with HIV RNA plasma viral load response below 500 copies/ml among 739 participants first prescribed any triple combination antiretroviral therapy

Variables	Unadjusted odds ratio	95% confidence intervals	*P*-value	Adjusted odds ratio	95% confidence intervals	*P*-value
Model						
Sex (male vs female)	2.09	1.35–3.25	0.001	1.18	0.72–1.95	0.508
95% adherence (yes vs no)	6.42	4.62–8.92	<0.001	5.67	4.06–7.97	<0.001
IDU (yes vs no)	0.49	0.35–0.68	<0.001	0.65	0.45–0.95	0.024
Age (10 year increments)	1.40	1.17–1.67	<0.001	1.29	1.03–1.53	0.023

response to ART [21]. Indeed, the present population-based study finds little evidence of a sex difference in the potential to achieve a virological response to treatment.

At baseline, we saw no significant difference in median plasma HIV RNA levels between the sexes. As this is an observational study of only those people accessing treatment, this finding is not surprising. More importantly, however, we found that plasma HIV RNA levels at baseline did not predict viral load suppression after 1 year of antiretroviral therapy in men or women, nor did viral load suppression to below 500 copies/ml differ by sex in participants who were 95% adherent to treatment. Thus, initial viral load, and male or female sex do not appear to predict the potential to suppress viral load in our population.

Older participants in our cohort were more likely to suppress viral load after 1 year of treatment. This may reflect survivor bias or, we postulate, that this trend may be explained in large part by the fact that slightly older participants were more adherent to treatment. These results are similar to other study findings that older participants tend to have better adherence to ART [44,45], and we suspect thus may reflect more stable lifestyles, social support and generally better overall health.

In our study population, only 59.4% of participants were 95% adherent to treatment. Very little adherence data have been reported among observational rather than clinical trial cohorts, and these observational results are consistent with other published reports [45,46]. Sub-optimal adherence has been suggested as the leading cause of virological failure of antiretroviral therapy [47].

Although a discrete sex difference in response to treatment fell from statistical significance in our multivariate model, our sub-analysis investigating adherence showed that women are less adherent to antiretroviral treatments than men, and women who inject drugs (most of HIV-infected women in our sample) have the most difficulty with treatment adherence. Therefore, women in our study have many of the characteristics that would predict that they will be among the least likely to succeed in suppressing viral load after at least 1 year of follow-up.

Even after controlling for adherence, injecting drugs predicted virological failure in our cohort. The frequency of transmission of drug-resistant HIV within the population of injection drug users in Vancouver has been found to be extremely low [49], thus we do not believe that drug resistance at baseline was a likely confounder in this study. However, HIV-infected injection drug users often present with a complicated array of medical and psychosocial issues. Indeed, injection drug users in Vancouver are less likely to have stable housing or reliable access to food and shelter than non-injection drug users, which may reflect a disorganized lifestyle and generally poorer health status [50]. Collection of more detailed psychosocial and medical information (that is, concurrent mental illness, co-infection with hepatitis C virus) may help to further explain the disparity in viral load suppression between users and non-users in our cohort in spite of similar quantitative markers of HIV disease.

Table 4. Sub-analysis of adherence

Variables	95% adherent	Non-adherent	*P*-value
Median age	37.5	35.7	<0.001
Women	32 (34.8%)	60 (65.2%)	0.001
Men	407 (62.9%)	240 (37.1%)	
PVL-suppressed			
Total number of women	24 (55.8%)	19 (44.2%)	0.002
Total number of men	325 (77.6%)	94 (22.4%)	
Not suppressed			
Total number of women	8 (16.3%)	41 (83.7%)	0.008
Total number of men	82 (36.0%)	146 (64.0%)	
IDU			
Total number of IDU-women	11 (26.8%)	30 (73.2%)	0.013
Total number of IDU-men	79 (48.5%)	84 (51.5%)	
Non-IDU			
Total number of non-IDU-women	21 (41.2%)	30 (58.8%)	0.001
Total number of non-IDU-men	328 (67.8%)	156 (32.2%)	

(row percentages presented).

This is one of the first population-based investigations of sex differences in virological response to antiretroviral therapy. Our study findings may therefore be more reflective of 'real life' trends as compared to results from clinical trials. The present study was carried out within a province-wide treatment programme in which all individuals theoretically have access to medical attention, treatment and laboratory monitoring free of charge. Also, the study is based on treatment-naive participants; therefore, our results are not confounded by previous therapy use. Finally, our attention to adherence in a sub-analysis was unique and underlines the fact that adherence remains one of the major obstacles for marginalized populations with respect to treatment success.

Our study may have been limited in a number of ways. Firstly, the number of women was relatively small; this reduces statistical power and the likelihood of detecting statistically significant differences. Also, our measure of adherence was based on prescriptions dispensed. One major problem in studying adherence is the lack of a standard measurement [48]. In the case of

prescription fills, physicians may have prescribed medications that were picked up but not taken and therefore, some participants may not have achieved viral load suppression despite filling each prescription. We suspect this may only confer a conservative bias to our results, and this measure of adherence has previously been shown to accurately predict adherence effects on viral load suppression [31].

Clinical outcomes other than viral load are presently being evaluated in our population. These are especially important to investigate, as a recent study evaluating sex and clinical outcomes after starting HAART in the UK found that women tended to have equal or even slightly better clinical outcomes than men after initiating HAART, as measured by hospital admissions, and development of a new AIDS-defining illness or death [51]. There was no statistically significant difference in the proportion of men and women on protease inhibitor- and non-nucleoside reverse transcriptase inhibitor-containing regimens in this study. This is important to consider in exploring both virological response as well as adherence to treatment, as both protease inhibitors and non-nucleoside reverse transcriptase inhibitors have been associated with particular side effects. We did not capture data regarding adverse effects, including depression. Sex may modify the risk of adverse events and tolerance with certain antiretroviral medications, and women have been found in some settings to suffer more acutely from side effects [52] and from depression [53]. Finally, non-injection drug use (such as crack cocaine) may affect adherence. These issues warrant further study in this population.

In summary, our results demonstrate that sex-related differences in the suppression of plasma HIV RNA to below 500 copies/ml after 1 year of antiretroviral therapy are readily explained by known confounders such as age, adherence and injection drug use. However, as women in our sample were on average younger, poorly adherent to treatment and injecting drugs, they were least likely to suppress viral load after 1 year. Although these data do not allow us to address the specific reasons why women and injection drug users in our study cohort did poorly and had difficulty adhering to their treatment regimens, our results do suggest an immediate need for greater efforts to promote treatment adherence, as well as further initiatives to identify and remove barriers to successful treatment for younger people, injection drug users and especially women.

Acknowledgements

We thank Bonnie Devlin, Diane Campbell, Elizabeth Ferris, Nada Gataric, Kelly Hsu, Myrna Reginaldo and Peter Vann for their research and administrative assistance.

Source of support

This work was supported by the National Health Research Development Programme of Health Canada through a National Health Research Scholar Award to Dr Hogg.

References

1. Carpenter CC, Cooper DA, Fischl MA, Gatell JM, Gazzard BG, Hammer SM, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS society – USA Panel. *Journal of the American Medical Association* 2000; **283(3):**381–390.
2. Hogg RS, Yip B, Kully C, Craib KJ, O'Shaugnessy MV, Schechter MT & Montaner JS. Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens. *Canadian Medical Association Journal* 1999; **160(5):**659–665.
3. Montaner JS, Montessori V, Harrigan R, OS M & Hogg R. Antiretroviral therapy: 'the state of the art'. *Biomedicine & Pharmacotherapy* 1999; **53(2):**63–72.
4. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, Kingsley LA, Todd JA, Saah AJ, Detels R, Phair JP & Rinaldo CR Jr. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Annals of Internal Medicine* 1997; **126(12):**946–954.
5. Fowler MG, Melnick SL & Mathieson BJ. Women and HIV. Epidemiology and global overview. *Obstetrics & Gynecology Clinics of North America* 1997; **24(4):**705–729.
6. Sterling TR, Lyles CM, Vlahov D, Astemborski J, Margolick JB & Quinn TC. Sex differences in longitudinal human immunodeficiency virus type 1 RNA levels among seroconverters. *Journal of Infectious Diseases* 1999; **180(3):**666–672.
7. Sterling TR, Vlahov D, Astemborski J, Hoover DR, Margolick JB & Quinn TC. Initial plasma HIV-1 RNA levels and progression to AIDS in women and men. *New England Journal of Medicine* 2001; **344(10):**720–725.
8. Moroni M. Sex differences in HIV-1 viral load and progression to AIDS. *Lancet* 1999; **353(9152):**589–590.
9. Junghans C, Ledergerber B, Chan P, Weber R & Egger M. Sex differences in HIV-1 viral load and progression to AIDS. *Lancet* 1999; **353(9152):**589.
10. Katzenstein DA, Hammer SM, Hughes MD, Gundacker H, Jackson JB, Fiscus S, Rasheed S, Elbeik T, Reichman R, Japour A & Merigan TC. The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. *New England Journal of Medicine* 1996; **335(15):**1091–1098.
11. Farzadegan H, Hoover DR, Astemborski J, Lyles CM, Margolick JB, Markham RB, Quinn TC & Vlahov D. Sex differences in HIV-1 viral load and progression to AIDS. *Lancet* 1998; **352(9139):**1510–1514.
12. Evans JS, Nims T, Cooley J, Bradley W, Jagodzinski L, Zhou S, Melcher GP, Burke DS & Vahey M. Serum levels of virus burden in early stage human immunodeficiency virus type 1 disease in women. *Journal of Infectious Diseases* 1997; **175(4):**795–800.
13. Delmas MC, Jadand C, De Vincenzi I, Deveau C, Persoz A, Sobel A, Kazatchkine M, Brunet JB & Meyer L. Gender difference in CD4+ cell counts persist after HIV-1 infection. *AIDS* 1997; **11(8):**1071–1073.
14. Prins M, Robertson JR, Brettle RP, Aguado IH, Broers B, Boufassa F, Goldberg DJ, Zangerle R, Coutinho RA & van den Hoek A. Do gender differences in CD4 cell counts matter? *AIDS* 1999; **13(17):**2361–2364.

15. Melnick SL, Sherer R, Louis TA, Hillman D, Rodriguez EM, Lackman C, Capps L, Brown LS Jr, Carlyn M & Korvick JA. Survival and disease progression according to gender of patients with HIV Infection. The Terry Beirn Community Programs for Clinical Research on AIDS. *Journal of the American Medical Association* 1994; **272(24):**1915–1921.
16. Cozzi Lepri A, Pezzotti P, Dorrucci M, Phillips AN & Rezza G. HIV disease progression in 854 women and men infected through injecting drug use and heterosexual sex and followed for up to nine years from seroconversion. *British Medical Journal* 1994; **309(6968):**1537–1542.
17. Chaisson RE, Keruly JC & Moore RD. Race, sex, drug use, and progression of human immunodeficiency virus disease. *New England Journal of Medicine* 1995; **333(12):**751–756.
18. Moore RD, Cheever L, Keruly JC & Chaisson RE. Lack of sex difference in CD4 to HIV-1 RNA viral load ratio. *Lancet* 1999; **353(9151):**463–464.
19. Bush CE, Donovan RM, Markowitz N, Baxa D, Kvale P & Saravolatz LD. Gender is not a factor in serum human immunodeficiency virus type 1 RNA levels in patients with viremia. *Journal of Clinical Microbiology* 1996; **34(4):**970–972.
20. Ellerbrock TV, Bush TJ, Chamberland ME & Oxtoby MJ. Epidemiology of women with AIDS in the United States, 1981 through 1990. A comparison with heterosexual men with AIDS. *Journal of the American Medical Association* 1991; **265(22):**2971–2975.
21. Zorilla CD. Antiretroviral combination therapy in HIV-1 infected women and men: are their responses different? *International Journal of Fertility* 2000; **45:**195–199.
22. Gersten M, Chapman S, Farnsworth A, Chang Y, Yu G & Clendeninn N. The safety and efficacy of Viracept (nelfinavir mesylate, NFV) in female patients participated in pivotal Phase II/III double-blind randomized controlled trials. *Conference on Women & HIV*. Pasadena, Calif., USA, May 4–7, 1997; 1.
23. Leavitt R, Lewi DS, Uip D, Pedro R, Kalichman A & Suleiman J. Subgroup analysis of clinical and surrogate marker efficacy by gender in a study of indinavir (IDV) alone and zidovudine (ZDV) in treatment naive HIV-1 patients with 50–250 CD4 cells/mm^3. *12th World AIDS Conference*. Geneva, Switzerland, June 28–July 3 1998; 60358.
24. Squires K, Gulick R, Pavia A, Eron J, Murphy R, Mauney J *et al.* Sex differences in the selection of thymidine analog regimen therapy trials (START I and START II). *7th Conference on Retroviruses & Opportunistic Infections*. Geneva, Switzerland, 2000.
25. Lemp GF, Hirozawa AM, Cohen JB, Derish PA, McKinney KC & Hernandez SR. Survival for women and men with AIDS. *Journal of Infectious Diseases* 1992; **166(1):**74–79.
26. Montaner J & O'Shaugnessy M. *Therapeutic Guidelines for the Treatment of HIV/AIDS and Related Conditions. Vancouver: BC Centre for Excellence in HIV/AIDS*; 1996.
27. Carpenter CC, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JS, Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S, Yeni PG & Volberding PA. Antiretroviral therapy for HIV infection in 1997. Updated recommendations of the International AIDS Society–USA panel. *Journal of the American Medical Association* 1997; **277(24):**1962–1969.
28. Carpenter CC, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JS, Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S, Yeni PG & Volberding PA. Antiretroviral therapy for HIV infection in 1998: updated recommendations of the International AIDS Society–USA Panel. *Journal of the American Medical Association* 1998; **280(1):**78–86.
29. World Health Organization. Acquired immune deficiency syndrome (AIDS): interim proposal for a WHO staging system for HIV infection and disease. *Weekly Epidemiological Record* 1990; **65:**221–228.
30. Carpenter CC, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Carpenter CC, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JS, Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S, Yeni PG & Volberding PA. Antiretroviral therapy for HIV infection in 1996. Recommendations of an international panel. International AIDS Society–USA. *Journal of the American Medical Association* 1996; **276(2):**146–154.
31. Low-Beer S, Yip B, O'Shaugnessy MV, Hogg RS & Montaner JSG. Adherence to triple therapy and viral load response. *Journal of Acquired Immune Deficiency Syndromes* 2000; **23:**360–361.
32. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, Wagener MM & Singh N. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine* 2000; **133(1):**21–30.
33. Kitahata MM, Van Rompaey SE & Shields AW. Physician experience in the care of HIV-infected persons is associated with earlier adoption of new antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes* 2000; **24(2):**106–114.
34. Phillips AN, Staszewski S, Weber R, Kirk O, Francioli P, Miller V, Vernazza P, Lundgren JD & Ledergerber B for the Swiss HIV Cohort Study, the Frankfurt HIV Clinic Cohort, and the EuroSIDA Study Group. HIV viral load response to antiretroviral therapy according to baseline CD4 cell count and viral load. *Journal of the American Medical Association* 2001; **286:**2560–2567.
35. Ledergerber B, Egger M, Opravil M, Telenti A, Hirshel B, Battegay M, Vernazza P, Sudre P, Flepp M, Furrer H, Francioli P & Weber R, for the Swiss HIV Cohort Study. Clinical Progression and virologic failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. *Lancet* 1999; **353:**863–868.
36. Kalish LA, Collier AC, Flanigan TP & Kumar P. Plasma viral load in women and men with advanced HIV disease. *39th Interscience Conference on Antimicrobial Agents & Chemotherapy*. San Francisco, Calif., USA, September 26–29 1999.
37. Collaborative Group on AIDS Incubation & HIV Survival. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly active antiretroviral therapy: a collaborative re-analysis. *Lancet* 2000; **355:**1131–1137.
38. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ & Holmberg SD. Declining morbidity and mortality among patients with advanced human immunodeficiency virus. *New England Journal of Medicine* 1998; **338(13):**853–860.
39. Thurmann PA & Hompesch BC. Influence of gender on the phamacokinetics and pharmacodynamics of drugs. *International Journal of Clinical Pharmacology & Therapeutics* 1998; **36(11):**586–590.
40. Hader S, Smith D, Moore J & Holmberg S. HIV infection in women in the United States: status at the millenium. *Journal of the American Medical Association* 2001; **285:**1186–1192.
41. Musey L, Hughes J, Schacker T, Shea T, Corey L & McElrath MJ. Cytotoxic-T-cell responses, viral load, and disease progression in early human immunodeficiency virus type 1 infection. *New England Journal of Medicine* 1997; **337(18):**1267–1274.
42. Ray SC & Quinn TC. Sex and the genetic diversity of HIV-1. *Nature Medicine* 2000; **6(1):**23–25.
43. Long EM, Martin HL Jr, Kreiss JK, Rainwater SM, Lavreys L, Jackson DJ, Rakwar J & Mandaliya K. Gender differences in HIV-1 diversity at time of infection. *Nature Medicine* 2000; **6(1):**71–75.
44. Mehta S, Moore RD & Graham NM. Potential factors affecting adherence with HIV therapy. *AIDS* 1997; **11(14):**1665–1670.
45. Gordillo V, del Amo J, Soriano V & Gonzalez-Lahoz J. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS* 1999; **13(13):**1763–1769.

46. Rodriguez-Rosado R, Jimenez-Nacher I, Soriano V, Anton P & Gonzalez-Lahoz J. Virological failure and adherence to antiretrovial therapy in HIV-infected patients. *AIDS* 1998; **12(9):**1112–1113.

47. Gross R, Bilker WB, Friedman HM & Strom BL. Effect of adherence to newly initiated antiretroviral therapy on plasma viral load. *AIDS* 2001; **15(16):**2109–2117.

48. Miller L & Hays R. Adherence to combination antiretroviral therapy: synthesis of the literature and clinical implications. *The AIDS Reader* 2000; **10(3):**177–185.

49. Alexander CS, Dong W, Schechter MT, O'Shaugnessy MV, Strathdee SA, Mo T, Montaner JSG & Harrigan PR. Prevalence of primary HIV drug resistance among seroconverters during an explosive outbreak of HIV among injection drug users. *AIDS* 1999; **13(8):**981–985.

50. Palepu A, Strathdee SA, Hogg RS, Anis AH, Rae S, Cornelisse PG, Patrick DM, O'Shaughnessy MV & Schechter MT. The social determinants of emergency department and hospital use by injection drug users in Canada. *Journal of Urban Health* 1999; **76(4):**409–418.

51. Moore AL, Sabin CA, Johnson MA & Phillips AN. Gender and clinical outcomes after starting highly active antiretroviral treatment: a cohort study. *Journal of Acquired Immune Deficiency Syndromes* 2002; **29(2):**197–202.

52. Moore RD, Fortgang I, Keruly J & Chaisson RE. Adverse events from drug therapy for human immunodeficiency disease. *American Journal of Medicine* 1996; **101(1):**34–40.

53. Ickovics JR, Hamburger ME, Vlahov D, Schoenbaum EE, Schuman P, Boland RJ & Moore J; HIV Epidemiology Research Study Group. Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study. *Journal of the American Medical Association* 2001; **285(11):**1466–1474.

Received 4 October 2002; accepted 12 August 2003