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SHORT COMMUNICATION

# Gender inequalities in the response to combination antiretroviral therapy over time: the Swiss HIV Cohort Study*

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**Objectives**

Gender-specific data on the outcome of combination antiretroviral therapy (cART) are a subject of controversy. We aimed to compare treatment responses between genders in a setting of equal access to cART over a 14-year period.

**Methods**

Analyses included treatment-naïve participants in the Swiss HIV Cohort Study starting cART between 1998 and 2011 and were restricted to patients infected by heterosexual contacts or injecting drug use, excluding men who have sex with men.

**Results**

A total of 3925 patients (1984 men and 1941 women) were included in the analysis. Women were younger and had higher CD4 cell counts and lower HIV RNA at baseline than men. Women were less likely to achieve virological suppression < 50 HIV-1 RNA copies/mL at 1 year (75.2% versus 78.1% of men; $P = 0.029$) and at 2 years (77.5% versus 81.1%, respectively; $P = 0.008$), whereas no difference between sexes was observed at 5 years (81.3% versus 80.5%, respectively; $P = 0.635$). The probability of virological suppression increased in both genders over time (test for trend, $P < 0.001$). The median increase in CD4 cell count at 1, 2 and 5 years was generally higher in women during the whole study period, but it gradually improved over time in both sexes ($P < 0.001$). Women also were more likely to switch or stop treatment during the first year of cART, and stops were only partly driven by pregnancy. In multivariate analysis, after adjustment for sociodemographic factors, HIV-related factors, cART and calendar period, female gender was no longer associated with lower odds of virological suppression.

**Conclusions**

Gender inequalities in the response to cART are mainly explained by the different prevalence of socioeconomic characteristics in women compared with men.

**Keywords:** HIV/AIDS, gender differences, women, antiretroviral therapy, outcome

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## Introduction

World-wide, more than 50% of people living with HIV/AIDS are women [1]. Despite large gender differences in terms of drug metabolism, pharmacokinetics, toxicity [2,3], and psychosocial factors that may affect access to treatment and outcome of combination antiretroviral therapy (cART), current treatment guidelines are based on data from clinical trials where women were clearly underrepresented [4,5]. Significant differences between the sexes were shown regarding tolerability [6,7] and drug levels of cART [2]. Apart from those for nevirapine, none of these differences have made their way into clinical guidelines [8–10]. Moreover, the potential for pregnancy should be considered when prescribing cART in women of childbearing age.

To date, conflicting results on the impact of gender on the response to cART have been reported from longitudinal studies, ranging from no differences between sexes [4,11–14] to a more favourable outcome for women [15–17] or men [18]. The discrepant results may be explained by the large variability in the study population [which included treatment-naïve or experienced patients, injecting drug users or men who have sex with men (MSM), and patients with differing access to medical care, type of antiretroviral therapy, length of follow-up] and with small sample size, often resulting in underpowered studies to investigate the gender issue.

The aims of this study were to compare the outcomes of cART in terms of virological suppression, immunological recovery and treatment modification between genders in a setting of equal access to care, and to explore changes over time.

## Methods

### Study population

Antiretroviral-naïve HIV-infected adults participating in the Swiss HIV Cohort Study (SHCS) who started cART between 1 January 1998 and 31 December 2011 with available HIV viral load and CD4 cell counts at 12 months and a potential follow-up of 24 months were eligible for inclusion in this study. We excluded MSM, restricting our analysis to women and men infected through injecting drug use or heterosexual contacts, because we aimed to compare men and women with similar lifestyles. We defined cART as an antiretroviral regimen containing at least three drugs, that is, two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a nonnucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) or integrase inhibitor, or three NRTIs.

### Study design

For this analysis we used data from the SHCS [19], a large prospective cohort study with continuous enrolment of adult HIV-infected individuals. A unique feature of the SHCS is the large proportion of women (30% of patients followed up in 2012 were women, compared with 24% in the European HIV cohort study (EuroSIDA), 24% in the AIDS Therapy Evaluation Project in Neatherland (ATHENA), 25% in the French HIV cohort study AQUITAINE and 18% in the Canadian HAART Observational Medical Evaluation and Research study (HOMER) cohort studies). Basic sociodemographic characteristics (year of birth, sex, HIV transmission risk, ethnicity and highest completed educational degree) and data on the clinical course (occurrence of opportunistic infections and death), coinfection with hepatitis B and C viruses (HBV and HCV, respectively), antiretroviral treatment, and immunological and virological parameters are collected at enrolment in the study and every 6 months thereafter on standardized data collection forms. AIDS-defining diseases are recorded using the 1993 revised clinical definition of AIDS from the Centers for Disease Control and Prevention [20]. Low educational status was defined as having no completed school or professional education or having completed mandatory school (9 years in Switzerland). For the present analysis we used the SHCS database extract of July 2013.

### Statistical analysis

The primary endpoint was the proportion of patients achieving virological suppression < 50 HIV-1 RNA copies/mL at 12 months after starting cART. Secondary endpoints were the proportion of patients achieving virological suppression < 50 copies/mL at 2 and 5 years, immunological recovery, defined as the median increase in CD4 cell count from baseline, and the proportion of patients switching or stopping cART at 12 months. Basic sociodemographic characteristics, CD4 cell count, HIV viral load, and cART were compared using the $\chi^2$ test or Fisher's exact test for categorical variables, and the Mann–Whitney or Kruskal–Wallis test for continuous variables. Logistic regression was used to explore predictors of achieving virological suppression at 1, 2 and 5 years. Multiple linear regression models were used to estimate the increase in CD4 cell count from baseline. Changes over time were investigated according to three calendar periods of starting cART, i.e. 1998–2001, 2002–2006 and 2007–2011.

All analyses were performed using STATA™ software version 11 for Windows (Stata Corp, College Station, TX).

 

## Results

### Study population

Between 1998 and 2011, 7440 treatment-naïve HIV-infected individuals participating in the SHCS started cART. We excluded 2922 patients because HIV transmission occurred among MSM, 465 patients (48% of these were women) because their viral load was not available at 1 year (10% of these because of death within the first year; 30% because of loss to follow-up), and an additional 128 patients because antiretroviral treatment did not correspond to our definition of cART. The present analysis was therefore performed with 3925 patients, i.e. 1984 (50.5%) men and 1941 (49.5%) women. During the study period there were 391 pregnancies, of which 290 occurred during the first year of treatment. Baseline characteristics of the study population according to sex and calendar period are summarized in Table 1. Women were younger, more often of non-white ethnicity, less educated, less likely to be injecting drug users, and started cART at higher CD4 cell counts and lower HIV viral loads than men.

### Outcome

Virological suppression < 50 copies/mL was achieved by 3009 of 3925 patients (76.7%) at 1 year, 2753 of 3472 patients (79.39%) at 2 years, and 16929 of 2091 patients (80.9%) with available follow-up data at 5 years (Table 1). Compared with men, women were less likely to achieve HIV RNA < 50 copies/mL at 1 year (75.2% versus 78.1% of men; $P = 0.029$) and at 2 years (77.5% versus 81.1%, respectively; $P = 0.008$), whereas no difference between the sexes was observed at 5 years of follow-up (81.3% versus 80.5%, respectively; $P = 0.635$). The probability of achieving virological suppression at 1, 2 and 5 years increased in both genders over time (test for trend, $P < 0.001$). A statistical interaction between virological suppression and gender was excluded by likelihood ratio test. The median increase in CD4 cell counts from baseline at 1, 2 and 5 years slowly increased over time, and was generally higher in women compared with men during the whole study period (Table 1). Similar results were obtained even if pregnant women ($n = 290$) were excluded, possibly because of the relatively low number of pregnant women in our study population. Overall, 1892 patients (48.2%) modified their initial cART regimen during the first year of treatment. Of these, 1530 patients switched to a new antiretroviral regimen and 362 discontinued cART for at least 3 months. Women were more likely to modify their treatment at 1 year (53.0% versus 43.5% of men; $P < 0.001$), even if pregnant women, who generally stop their treatment after delivery, were excluded. The most frequent reason for women to modify their therapy within the first year was toxicity (15% of all women starting cART compared with 13% of men), followed by physician's decision and patient's wish. The most common toxicities in women were gastrointestinal intolerance (34%), followed by adverse events involving the central nervous system (26%) and hypersensitivity reactions (21%), whereas men most frequently reported symptoms related to the gastrointestinal system (35%), central nervous system (32%) and hypersensitivity (11%). These differences were not statistically significant ($P = 0.198$).

In univariate analysis, virological suppression at 1 year (Table 2) was associated with male gender, older age, white ethnicity, higher education, lower HIV RNA and CD4 cell counts at cART initiation, NNRTI-based regimens, not being an injecting drug user or coinfected with HCV, and starting cART in more recent years. In multivariate analysis, after adjustment for sociodemographic factors, HIV-related factors, cART and calendar period, gender, education and coinfection with HCV were no longer associated with virological suppression. Independent predictors for achieving HIV RNA < 50 copies/mL at 1 year were starting cART in more recent years [odds ratio (OR) 2.74; 95% confidence interval (CI) 2.21–3.40, for the calendar period 2007–2011 compared with 1998–2001] and treatment with an NNRTI-based regimen (OR 1.82; 95% CI 1.51–2.20, compared with a PI-based regimen), while injecting drug use (OR 0.57; 95% CI 0.44–0.74), non-white ethnicity (OR 0.75; 95% CI 0.61–0.93) and higher HIV viral load at cART initiation (OR 0.75; 95% CI 0.63–0.90) were associated with lower odds of virological suppression at 1 year. Similar findings were noted for virological suppression at 2 and 5 years.

Women showed a better immunological recovery at 1 year (median CD4 count increase from baseline of 170 cells/μL; 95% CI 78–269 cells/μL) than men (median 140 cells/μL; 95% CI 64–247 cells/μL; $P < 0.001$). After adjustment for socioeconomic factors, HIV stage, CD4 cell count at baseline, viral load at 1 year, coinfection with HCV, cART and calendar period, independent predictors of better CD4 cell count increase from baseline at 1 year were female gender (median 17 cells/μL; 95% CI 5–29 cells/μL), virological suppression at 1 year (median 59 cells/μL; 95% CI 45–73 cells/μL) and starting cART in more recent years (median 35 cells/μL; 95% CI 20–50 cells/μL), whereas older age (median −15 cells/μL; 95% CI −21 to −9 cells/μL, per 10-year increase), lower CD4 cell count at baseline (median −15 cells/μL; 95% CI −18 to −12 cells/μL, per 100 cells/μL), cART based on NNRTI compared with PI (median −19 cells/μL; 95% CI −31 to −7 cells/μL), injecting drug use (median −49 cells/μL; 95 CI% −67 to −30 cells/μL) and non-white ethnicity (median −35 cells/μL; 95% CI −49 to −21 cells/μL) were associated with lower CD4 cell count increase. Similar trends were observed for immunological recovery at 2 and 5 years.

**Table 1** Baseline characteristics and outcomes of the study population ($n = 3925$) according to sex and calendar period of starting combination antiretroviral therapy (cART)

| | Calendar period 1998–2001 | | | Calendar period 2002–2006 | | | Calendar period 2007–2011 | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Women ($n = 599$) | Men ($n = 680$) | *P*-value | Women ($n = 685$) | Men ($n = 647$) | *P*-value | Women ($n = 670$) | Men ($n = 666$) | *P*-value |
| Age [median (IQR)] | 34 (29–38) | 38 (33–44) | <0.001 | 34 (29–41) | 40 (33–48) | <0.001 | 36 (30–44) | 41 (34–49) | <0.001 |
| Non-white ethnicity [*n* (%)] | 243 (40.6%) | 115 (16.9%) | <0.001 | 370 (54.0%) | 124 (19.2%) | <0.001 | 348 (53.0%) | 176 (26.89%) | <0.001 |
| Lower educational level [*n* (%)] | 98 (17.1%) | 63 (9.6%) | <0.001 | 98 (14.3%) | 70 (10.8%) | 0.063 | 91 (13.7%) | 51 (7.7%) | <0.001 |
| Prior AIDS-defining disease [*n* (%)] | 105 (17.5%) | 156 (22.9%) | 0.017 | 121 (17.7%) | 152 (23.5%) | 0.008 | 113 (17.2%) | 118 (18.0%) | 0.717 |
| Injecting drug use [*n* (%)] | 143 (23.9%) | 259 (38.1%) | <0.001 | 94 (13.7%) | 169 (26.1%) | <0.001 | 63 (9.6%) | 122 (18.6%) | <0.001 |
| CD4 count (cells/μL) [median (IQR)] | 199 (83–355) | 185 (66–330) | 0.042 | 208 (110–292) | 176 (80–271) | <0.001 | 264 (153–358) | 240 (129–334) | 0.012 |
| HIV RNA > 100 000 copies/mL [*n* (%)] | 213 (35.6%) | 271 (39.9%) | 0.221 | 231 (33.7%) | 276 (42.7%) | <0.001 | 152 (24.7%) | 210 (34.4%) | <0.001 |
| HCV coinfection [*n* (%)] | 151 (22.0%) | 232 (35.9%) | <0.001 | 152 (21.9%) | 237 (35.6%) | <0.001 | 111 (17.0%) | 171 (26.0%) | <0.001 |
| cART [*n* (%)] | | | | | | | | | |
| Boosted PI-based | 425 (70.9%) | 508 (74.7%) | 0.320 | 343 (50.1%) | 302 (46.7%) | 0.441 | 408 (62.1%) | 335 (51.0%) | <0.001 |
| NNRTI-based | 149 (24.9%) | 147 (21.6%) | | 314 (45.8%) | 319 (49.3%) | | 231 (35.2%) | 306 (46.6%) | |
| Other | 25 (4.2%) | 25 (3.7%) | | 28 (4.1%) | 26 (4.0%) | | 18 (2.7%) | 16 (2.4%) | |
| HIV RNA < 50 copies/mL at 1 year [*n* (%)] | 394 (65.8%) | 447 (65.7%) | 0.988 | 516 (75.3%) | 534 (82.5%) | 0.001 | 549 (83.6%) | 569 (86.6%) | 0.121 |
| HIV RNA < 50 copies/mL at 2 years* [*n* (%)] | 344 (64.5%) | 415 (70.2%) | 0.042 | 504 (79.8%) | 482 (83.4%) | 0.103 | 496 (87.0%) | 512 (90.1%) | 0.098 |
| HIV RNA < 50 copies/mL at 5 years** [*n* (%)] | 290 (72.0%) | 313 (72.5%) | 0.874 | 412 (86.0%) | 383 (85.9%) | 0.952 | 160 (89.9%) | 134 (87.6%) | 0.507 |
| CD4 increase at 1 year (cells/μL) [median (IQR)] | 150 (58–239) | 120 (38–228) | 0.020 | 167 (72–269) | 147 (68–248) | 0.186 | 184 (99–287) | 150 (82–262) | 0.005 |
| CD4 increase at 2 years (cells/μL) [median (IQR)]* | 192 (67–320) | 169 (66–305) | 0.365 | 213 (98–359) | 195 (110–314) | 0.384 | 251 (130–381) | 222 (125–350) | 0.134 |
| CD4 increase at 5 years (cells/μL) [median (IQR)]** | 243 (87–409) | 220 (96–392) | 0.607 | 312 (155–485) | 264 (143–410) | 0.013 | 322 (182–500) | 326 (200–460) | 0.610 |

HCV, hepatitis C virus; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
*Data at 2 years available for 3472 patients; **data at 5 years available for 2091 patients.

**Table 2** Predictors of achieving virological suppression < 50 copies/mL at 1 year after starting combination antiretroviral therapy (cART)

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variable | OR | 95% CI | *P*-value | OR[†] | 95% CI | *P*-value |
| Women compared with men | 0.83 | 0.72–0.96 | 0.012 | 0.87 | 0.73–1.04 | 0.127 |
| Age, per 10 years older | 1.22 | 1.14–1.32 | <0.001 | 1.04 | 0.96–1.14 | 0.329 |
| Non-white ethnicity | 0.91 | 0.79–1.06 | 0.234 | 0.75 | 0.61–0.93 | 0.009 |
| Injecting drug use | 0.55 | 0.47–0.65 | <0.001 | 0.57 | 0.44–0.74 | <0.001 |
| Prior AIDS-defining condition | 1.03 | 0.86–1.25 | 0.762 | 0.94 | 0.75–1.17 | 0.572 |
| Lower education level | 0.80 | 0.69–0.93 | 0.003 | 0.89 | 0.75–1.07 | 0.207 |
| HCV coinfection | 0.74 | 0.64–0.87 | <0.001 | 1.05 | 0.83–1.33 | 0.686 |
| CD4 count at cART initiation, per 100 cells/μl increase | 0.96 | 0.95–0.98 | <0.001 | 0.96 | 0.94–0.98 | <0.001 |
| HIV RNA > 100 000 copies/mL at cART initiation | 0.83 | 0.71–0.97 | 0.020 | 0.75 | 0.63–0.90 | 0.002 |
| cART based on | | | | | | |
| Boosted PI | 1* | – | – | 1* | – | – |
| NNRTI | 2.09 | 1.77–2.48 | <0.001 | 1.82 | 1.51–2.20 | <0.001 |
| Other | 1.24 | 0.83–1.86 | 0.288 | 1.41 | 0.90–3.39 | 0.135 |
| Calendar period | | | | | | |
| 1998–2001 | 1* | – | – | 1* | – | – |
| 2002–2006 | 2.01 | 1.69–2.38 | <0.001 | 1.65 | 1.35–2.01 | <0.001 |
| 2007–2011 | 3.11 | 2.58–3.75 | <0.001 | 2.74 | 2.21–3.40 | <0.001 |

CI, confidence interval; HCV, hepatitis C virus; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.
[†]Adjusted for all variables listed.
*Reference category.

## Discussion

This study, involving 3925 patients who started cART from 1998 to 2011 in a large cohort study, illustrates gender inequalities in the virological and immunogical response to cART, which were mainly explained by large differences in socioeconomic factors. Importantly, the outcome of cART in terms of virological response and immunological recovery improved in both genders over time.

Similarly to other cohorts [12,14,15,17,18,21–26], women starting cART were younger, were more frequently of non-white ethnicity, were less educated, and had higher CD4 cell counts and lower HIV RNA than men. In line with the findings of other studies [12,14,15,17,21,25,27], after adjustment for potential confounders, no major differences in virological suppression at 1, 2 and 5 years were observed between the sexes in a setting of equal access to cART. In multivariate analysis, among sociodemographic factors, only non-white ethnicity was an independent risk factor for not achieving virological suppression, suggesting that immigration (mainly from sub-Saharan Africa to Switzerland) may explain differences in virological suppression between the sexes. This finding is consistent with those of other studies [28–32], and is possibly a result of suboptimal adherence [32,33].

Although the outcome of cART improved in both genders over time, women achieved similar rates of virological suppression to men, with a certain delay, possibly reflecting safety concerns about the use of newer and more potent antiretroviral drugs in young women [34]. However, differences between sexes were decreased in recent years, possibly as a result of the increasing potency of new antiretrovirals. The less frequent prescription of NNRTIs in more recent years is probably attributable to concerns about the use of efavirenz in women of childbearing age [34]. In a subgroup analysis (data not shown), cART prescription including more recent drugs and response to treatment were similar in men and women older than 40 years. As previously reported [3], women were more likely to modify their cART because of drug toxicity or intolerance. This may be explained by biological differences and genetic factors influencing the pharmacokinetics of specific drugs and thus their plasma levels [3,16,35,36]. Also, sociocultural barriers, leading to different perceptions of drug-related adverse events, might play a role [37,38]. Furthermore, discontinuation of cART during the first year of treatment was more common in women, possibly because most patients stopped treatment following pregnancy.

In agreement with other studies [12,15–17,39,40], we observed a better immunological recovery in women, regardless of baseline CD4 cell count and type of cART. This observation is supported by higher CD4 cell counts in women than men among HIV-negative patients, and higher immune activation in the presence of HIV infection [41]. By contrast, several reports indicated similar increases in CD4 cell counts between the sexes [12,14,21]. However, discrepancies among these studies may be explained by differences in the study populations, with some studies including patients with different lifestyles such as MSM

[21], and lower proportions of women [12] precluding the detection of such small differences.

We acknowledge that the study has some limitations. Data on adherence to cART were not considered in the present analysis. We collected data on the first cART modification, but not on successive treatment changes that might have affected virological suppression and immunological recovery. However, most treatment modifications occurred during the first year, so this may not have had a large effect on the outcome. This study has several strengths. To our knowledge, this is the first study to address the issue of gender inequalities in a large number of treatment-naïve patients over a 14-year period in a setting of equal access to care. Moreover, a unique feature of the SHCS is the large proportion of women (> 30%).

In conclusion, gender inequalities in the response to cART are mainly explained by the different prevalences of socioeconomic characteristics in women compared with men.

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