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Research Paper

Sex differences in HIV treatment outcomes and adherence by exposure groups among adults in Guangdong, China: A retrospective observational cohort study

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ABSTRACT

Introduction: We aimed to assess sex differences in treatment outcomes and adherence comparing men who have sex with women (MSW), men who have sex with men (MSM), and women who have sex with men (WSM), as well as men and women who inject drugs living with HIV on combination antiretroviral therapy (ART) in Guangdong, China.

Methods: We performed a retrospective observational cohort study with data from the National Free Antiretroviral Treatment Program database. We included ART-naive patients aged 18 to 80 years who had contracted HIV through sex or injecting drugs, initiated first-line ART between January 2004 and December 2016, and had at least 60 days of follow-up. Participants were followed for five years. Kaplan-Meier analysis and Cox proportional hazard models were used to evaluate all-cause mortality. Cumulative incidence function and Cox proportional hazards models accounting for competing risks were used to evaluate disease progression to AIDS. Modified Poisson regression models were used to evaluate immunological and virological responses and loss to follow-up. Repeated measures analysis was used to evaluate regular CD4+ cell count, HIV viral load monitoring, ART adherence, side effects, and interruption of ART.

Findings: We included 26,409 persons living with HIV. 21,779 (82·5%) people acquired HIV through sex (5118 WSM [23·5%], 8506 MSW [39·0%], 8175 MSM [37·5%]), and 4610 people (17·5%) through injection drug use (249 women [5·4%], 4361 men [94·6%]). Among those infected through sex, MSW had increased risks of all-cause mortality (adjusted hazard ratio [aHR] 1·48, 95% CI 1·20–1·83), progression to AIDS (1·27, 1·09–1·47), virological failure (adjusted incidence rates ratio [aIRR] 1·27, 95% CI 1·09–1·48), and loss to follow-up (1·22, 1·10–1·35) compared to WSM. In contrast, MSM had lower risk of all-cause mortality (aHR 0·49, 95%CI 0·32–0·76), disease progression to AIDS (0·83, 0·68–1·00), and virological failure (aIRR 0·78, 95%CI 0·65–0·94), were more likely to receive regular CD4+ cell count (1·08, 1·07–1·10) and HIV viral load monitoring (1·13, 1·12–1·15), were less likely to report missing ART doses (0·54, 0·49–0·61), interrupt ART (0·34, 0·26–0·44), or be lost to follow-up (0·56, 0·49–0·65) compared to WSM. Men who inject drugs were almost twice as likely as women who inject drugs to die (aHR 1·72, 95%CI 1·03–2·85), experience disease progression to AIDS (2·05, 1·18–3·57), virological failure (aIRR 1·81, 95%CI 1·19–2·76), report ART side effects (1·78, 1·43–2·22), and interruptions in ART (2·29, 1·50–3·50).

Interpretation: Our findings highlight the importance of identifying potentially at-risk MSW and promoting HIV education and testing among them. Particular attention is warranted among men who inject drugs to

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improve timely HIV diagnosis, drug interaction management, and retention in treatment. Additional research from rural settings is needed to assess the long-term treatment outcomes and adherence in MSM with HIV.

Research in context

Evidence before this study

We searched PubMed, Google Scholar, and China National Knowledge Infrastructure for studies published in English and Chinese from Jan 1, 1998, to Feb 1, 2019. We used the search terms "HIV", or "AIDS", and "sex", or "gender". We found two systematic reviews showing that HIV-infected men treated with antiretroviral therapy (ART) have a higher risk of all-cause mortality compared to women. The majority of original studies found worse immunological and virological response and poorer retention in treatment in HIV-infected men than that in women. However, whether these differences observed comparing men and women overall differ by HIV exposure groups is unclear. Few studies compared treatment outcomes and adherence behaviors between male and female injection drug users, or among men who have sex with men (MSW), men who have sex with men (MSM), and women who have sex with men (WSM). These few studies have yielded conflicting results.

Added value of this study

Among people who had contracted HIV by sex, MSW had increased risks of all-cause mortality, disease progression to AIDS, and virological failure, and were more likely to be lost to follow-up compared to WSM. In contrast, MSM showed better treatment outcomes and compliance behaviors including regular testing for CD4+ cell count and viral load, adherence to treatment, and retention in treatment compared to WSM. In those infected through injecting drugs, men were almost twice as likely as women to die, experience disease progression to AIDS, virological failure, ART side effects, and interruptions in ART compared to women.

Implications of all the available evidence

Our study suggests that in higher middle-income country where ART coverage is high, MSW and men who inject drugs are likely to have poorer HIV treatment outcomes and adherence behaviors compared to WSM and women who inject drugs respectively. Among injection drug users, men are also more likely than women to experience ART side effects. MSM with HIV are more likely to show favorable treatment outcomes and adherence than WSM. Our findings highlight the importance of identifying potentially high-risk MSW (e.g., male migrant workers, older men from rural areas, and male sexual workers) and promoting HIV health education and testing among them. Particular focus on men who inject drugs is warranted in interventions to improve timely HIV diagnosis, drug interactions management, and retention in treatment among injection drug users. Additional studies from rural settings are needed to assess the long-term treatment outcomes adherence in MSM with HIV.

1. Introduction

The widespread use of antiretroviral therapy (ART) substantially extends the lifespan of people living with HIV and prevents HIV transmission [1]. Despite the effectiveness of ART, HIV/AIDS remains a leading cause of death globally, particularly in low- and middle-income countries [2]. The number of people living with HIV/AIDS (PLWHA) continues to rise, with high rates of transmission seen in at-risk populations, including men who have sex with men (MSM) and people who inject drugs (PWID) [3].

Differences in treatment outcomes between men and women living with HIV is a subject of debate and concern. A global systematic review and meta-analysis of 65 studies found a decreased risk of death among women living with HIV and on ART compared with men (pooled risk ratio [RR] 0·72, 95% confidence interval [CI] 0·69–0·75), but their differences in progression to AIDS and immunological and virological response were not significant [4]. Another systematic review and meta-analysis of 31 studies in low-and middle-income countries found a significantly higher risk of all-cause mortality among men living with HIV compared to women (pooled hazard ratio [HR] 1·46, 95% CI 1·53–1·59) [5]. Studies in Europe also reported better clinical, virological, and immunological responses to ART in women than in men [6–8]. Conversely, a study conducted in the United States found that women living with HIV suffered from a higher burden of diseases compared to men [9], and a multicenter cohort study in Canada showed that women had poorer HIV virological responses to ART [10]. Other studies in high-income settings have found no significant differences in outcomes between men and women [11–13].

Men and women have different patterns of HIV acquisition, which may explain potential differences in treatment adherence and outcomes. Several studies have reported that a higher proportion of men than women acquired HIV through injecting drugs [8,14,15]. PWID are a population which has been found to have poorer adherence to ART and higher mortality [7,16–18]. Additionally, MSM are a subset of men at higher risk of HIV infection. It remains unclear whether MSM living with HIV have different treatment outcomes and ART adherence compared with men who have sex with women (MSW) and women who have sex with men (WSM). A study from Brazil found increased HIV-related mortality among MSM compared to WSM [19], whereas a British study reported that MSM had a lower risk of virological failure than heterosexual people [20], and studies from China reported lower mortality but faster disease progression among MSM compared to other PLWHA [21,22]. In terms of ART adherence, a study from Kenya reported a higher percentage of MSM having less than 95% adherence to ART [23], but another study in Asia reported that ART adherence was better in MSM compared with heterosexual people [24].

In China, HIV-infected populations mainly consist of PWID, MSM, female sex workers, and former plasma donors or blood transfusion recipients [25]. Since the implementation of nationwide access to free ART in 2002, all-cause mortality has significantly reduced among former plasma donors living with HIV [26], but remains high among MSM and PWID [25]. Previous studies found lower all-cause mortality and better virological response to ART in Chinese women compared to Chinese men living with HIV [27,28], however it is unclear whether these differences remain among MSM, MSW, and WSM, and between male and female injection drug users.

To inform strategies to optimize ART delivery to at-risk populations, we report on differences in HIV treatment outcomes (i.e., survival, disease progression, immunological and virological responses), and adherence (i.e., regular CD4+ cell count and viral load monitoring, ART adherence, ART side effects, and retention in treatment) among MSW, MSM, and WSM as well as between men and women who inject drugs living with HIV/AIDS who were receiving ART in China.

2. Methods

2.1. Study design and participants

This study was reported according to the guideline of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE, see supplementary STROBE checklist) [29]. We performed a retrospective observational cohort study using data retrieved from the National Free Antiretroviral Treatment Program database. This database, which is managed by the National Center for AIDS/STD Control and Prevention, China Center for Disease Control and Prevention (China CDC), has been described elsewhere [25,30]. Each province, municipality, and autonomous region has access to data for its jurisdiction.

We included all patients living with HIV who were treated in hospitals in Guangdong Province between January 2004 and December 2016, between 18 and 80 years of age, and had not previously received ART. We excluded persons who contracted HIV through blood or plasma transfusion, perinatal transmission, or unknown route, had not started a first-line ART regimen recommended by national treatment guidelines, had fewer than 60 days of follow-up, and did not have CD4+ cell count records at baseline or follow-up. To minimize the potential misclassification of HIV exposure groups, we excluded those infected through sexual contact having a record of methadone use.

Chinese national guidelines for the treatment of HIV/AIDS have changed over time. Prior to 2007 those with a CD4+ count $\leq$ 200 cells per μL or who had been diagnosed with an AIDS-defining illness were eligible for ART initation [21,31]. The treatment initiation threshold was raised to 350 cells per μL in 2008 and then to 500 cells per μL in 2012 [21,32]. Since 2016 all PLWHA have been eligible for ART regardless of CD4+ count [33]. Before 2009 recommended first-line ART regimens were zidovudine or stavudine plus lamivudine and nevirapine or efavirenz [31]. Since 2010 stavudine has been replaced by tenofovir in national guidelines [31,32]. ART regimens were offered by the government to people living with HIV free of charge, so the availability of ART regimens has not varied over time. Similarly, the national recommendation in terms of the CD4+ cell count (at least twice per year) and virologic monitoring (at least twice per year) [34], which are also free of charge, has not changed over time.

This study was approved by the institutional review board of the Guangzhou Eighth People's Hospital.

2.2. Procedures

Baseline and follow-up information was assessed based on standardized case report forms that were uploaded to the central database. Details on data collection could be found elsewhere [30]. Baseline information measured at ART initiation included self-reported route of HIV acquisition, demographics (age, gender, marital status, residence), clinical and laboratory characteristics (WHO clinical staging of HIV disease, tuberculosis infection status, body weight, height, CD4+ cell counts, CD8 cell counts, HIV viral load, hemoglobin, HBsAg status, hepatitis C antibody status), date of HIV diagnosis, and initial ART regimen. Patients with a district, prefectural, or city address were considered to be urban and those with a countryside or village address to be rural. Information on clinical and laboratory characteristics, ART adherence, ART side effects, treatment interruption, and reasons for treatment interruption were collected at scheduled follow-up visits (0·5, 1, 2, and 3 months after ART initiation and every 3 months thereafter). Information regarding clinical and laboratory outcomes, treatment interruption, and reasons for treatment interruption was obtained by medical records. ART adherence was self-reported and collected by the following question asked by nurses: "How many times did you miss ART doses during the previous week?", then patients would reply by giving the specific number of times that they had missed ART does. Side effects of ART were also self-reported and collected by asking patients whether they had the following symptoms related with ART side effects (options were given): changes in appetite, vomiting, insomnia, abdominal pain, dry skin, skin rash, numbness or pain, fatigue, lipodystrophy, hair loss, vision change, headache, vivid dreams, or other.

We assessed five outcomes: clinical outcomes, immunological and virological responses, ART adherence, ART side effects, and retention in treatment. We assessed clinical outcome by all-cause mortality and disease progression from HIV to AIDS. Survival time was measured as date of ART initiation to date of death, date of last follow-up visit, or 31 December 2016, whichever came first, though maximum follow-up time was prespecified at 5 years. We determined the length of the maximum follow-up duration based on the number of patients retained in follow up in each group and clinical significance (supplementary method 1.1 and supplementary Figs. 1–3) [35]. We defined progression to AIDS according to the diagnostic criteria established by the United States Centers for Disease Control and Prevention [36]. We defined immunological responses to ART as a CD4+ count increase of more than 30% compared to baseline at 12 months after ART initiation. For those patients who did not receive CD4+ cell count testing at exactly 12 months following ART initiation, we selected the test result measured within nine to 15 months, the closest estimate to 12 months after ART initiation for analysis [31]. We also assessed immunological response by CD4+/CD8 ratio normalization, defined as two consecutive measurements of a CD4+/CD8 ratio $\geq$ 1 after initiating ART among patients with CD4+/CD8 ratio $<$0.8 at ART initation [37]. We defined adequate HIV viral suppression as a viral load of $<$ 400 copies per mL at 12 months after ART initiation. For those who did not receive viral load record testing at exactly 12 months after ART initiation, we selected the test result within six to 18 months, the closest estimate to 12 months after ART initiation for analysis. HIV virological failure was defined as one or more measurements of viral load $\geq$ 400 copies per mL, which was grouped in ranges of 400–999 copies per mL and $\geq$1000 copies per mL [31]. We assessed adherence by compliance to routine monitoring of CD4+ cell count (at least twice per year) [34], HIV viral load (at least once per year) [34], and self-reported missed ART doses during the previous week at each clinical visit. Retention in treatment was assessed by ART interruption and loss to follow-up. Patients were considered to be lost to follow-up if four successive follow-up appointments were missed [30]. Those who transferred care to another facility were not counted as loss to follow-up.

2.3. Statistical analysis

Differences in baseline characteristics and outcomes were compared between MSW, MSM, and WSW, and then between men and women who inject drugs. Differences in outcomes comparing men and women overall were also assessed. Each patient was classified as acquiring HIV through either injection drug use, homosexual contact (i.e., MSM), or heterosexual contact. We analyzed covariates measured at baseline including age, marital status (unmarried vs married), residence (urban vs rural), BMI ($<$18, 18–24, $\geq$24 kg/m2) [38], anemia (severe [hemoglobin $<$8·1 g/dL], moderate [8·1–$<$10 g/dL in women and 8·1–$<$11 g/dL in men], mild [10–$<$11·9 g/dL in women and 11–$<$13·1 g/dL in men], none [$\geq$11·9 g/dL in women and $\geq$13·1 g/dL in men]) [39], time between HIV diagnosis and ART initiation ($>$6 months vs $\leq$6 months), WHO clinical stage (III or IV vs I or II), hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection (yes vs no), the tuberculosis infection (yes vs no), ART regimen, and year of ART initiation. CD4+ cell counts was collected both at baseline and during follow-up as a longitudinal variable. Given that CD4+ cell counts can only have positive values and were possibly skewed, we

applied a base 10 logarithmic transformation to achieve normalization.

Baseline characteristics were compared using $\chi 2$ tests for categorical variables and Kruskal-Wallis test for continuous variables. To assess the stability of time-to-event estimates, we computed median follow-up time using a reverse Kaplan–Meier method [40–42]. We assessed all-cause mortality by sex with Kaplan–Meier analyses and performed log-rank tests for statistical comparisons. We used a cumulative incidence function within a competing risks framework to calculate the cumulative incidence of disease progression from HIV to AIDS (death without AIDS was considered as a competing event) and modified $\chi 2$ tests (Gray's test) for statistical comparisons [43,44]. We used Cox proportional hazard models to assess unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CI) for all-cause mortality and cause-specific Cox proportional hazard models for disease progression to AIDS. We tested adherence to the proportional hazard assumption by log-log survival plots. CD4+ cell counts were included in Cox models as a time-updated covariate. Covariates with $p<0{\cdot}1$ in univariate analysis were included in the initial adjusted model. The final adjusted model included all covariates with $p<0{\cdot}05$ in addition to age at ART initiation and time-updated CD4+ cell counts.

We used modified Poisson regression models with robust estimators [45] to assess unadjusted and adjusted incidence rate ratios (IRRs) with 95% CIs for immunological and virological response and loss to follow-up, as defined in the procedure section. We used repeated measures analysis with the generalized estimating equations method [46] to assess unadjusted and adjusted IRRs with 95% CIs for regular monitoring of CD4+ cell counts and HIV viral load, adherence to treatment, ART side effects, and ART interruption. Patients who died were excluded from the analysis of ART interruption and loss to follow-up. Covariates with $p<0{\cdot}1$ in univariate analysis were included in the initial adjusted model, and the final adjusted model included age and CD4+ cell counts at ART initiation, and all other covariates with $p<0{\cdot}05$.

We used multiple imputation by chained equation methods to impute (20 times) missing baseline data [47]. The imputation model included all measured variables in addition to primary outcomes (death status, progression to AIDS, and cumulative hazards) [48,49]. In sensitivity analyses we repeated the analysis of CD4+ cell count and virological response at 24 months after ART initiation, and survival, disease progression, CD4+/CD8 ratio normalization, and ART adherence before 24 months and after 24 months (as landmark time) after ART initiation respectively.

Statistical significance was set as a p value less than 0·05 for all analyses. Statistical analyses were performed using R version 3.5.1.

2.4. Role of the funding source

Study funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

3. Results

3.1. Participants selection and baseline characteristics

We retrieved data for 35,989 ART-naive persons aged 18 to 80 years old initiated ART in Guangdong Province between 2004 and 2016 (supplementary Fig. 4). 2536 (7·0%) patients (median age: 40, men: 71·0%) were excluded because they acquired HIV through an unknown route (2242), perinatal transmission (4), or blood or plasma transfusion (290). We also excluded 4149 (11·5%) patients (median age: 37, men: 72·8%) who were not started on a standard first-line ART regimen, 209 (0·6%) who reported acquiring HIV through sex but also had previously used methadone, 2461 (6·8%) who had fewer than 60 days of follow-up (median age: 36, men: 84·0%), and 225 (0·6%) without any recorded CD4+ count. A total of 26,409 patients, including 21,042 (79·7%) men and 5367 (20·3%) women, were included in our analysis. Of the total 26,409 patients, 21,799 (82·5%) reported acquiring HIV through sexual exposure (5118 WSM [23·5%], 8506 MSW [39·0%], and 8175 MSM [37·5%]), and 4610 (17·5%) reported acquiring HIV through injection drug use (249 women [5·4%] and 4361 men [94·6%]). The percentage of patients adhering to scheduled clinic visit every three month decreased over time but still remained above 75% in for fifth year after ART initiation (supplementary Fig. 5). Overall, a significantly higher proportion of men than women reported acquiring HIV through injection drug use (20·72% vs 4·64%, $p<0{\cdot}001$). Among those who acquired HIV through sex, median age at ART initiation was lowest for MSM (30 years) and highest for MSW (41 years). Median CD4+ cell counts and CD4+/CD8 ratio at ART initiation were highest among MSM, followed by WSM and MSW. Coinfection with HBV, HCV, and tuberculosis were most frequent in MSW. MSW also had the shortest time between HIV diagnosis and ART initiation. Compared with WSM and MSW, MSM were more likely to live in urban areas, be classified as WHO stage I or II, initiate ART after 2014, and receive a tenofovir-based ART regimen. BMI and hemoglobin were lower in WSM than in MSW and MSM. Among those who acquired HIV through injection drug use, men who had injected drugs had a higher BMI and hemoglobin, shorter time between HIV diagnosis and ART initiation, lower CD4+ cell counts and CD4+/CD8 ratio, and higher frequency of HBV or HCV co-infection compared to women (Table 1).

3.2. Death and progression to aids

Median follow-up was 22 months (IQR 10–44). Median follow-up for MSM was significantly shorter than that for WSM ($p<0{\cdot}001$, Table 2), but was similar between men and women who inject drugs (p = 0·8, Table 2). A total of 971 (3·68%) participants died from any cause during 58,220 person-years of follow-up. Overall, men had a higher risk of all-cause mortality than women (adjusted HR 1·78, 95% CI 1·49–2·14, p-value <0·001 Fig. 1, Table 2, supplementary Table 2). All-cause mortality was highest among men who inject drugs (16·85 [15·07–18·79] per 1000 person-years) and lowest among MSM (2·01 [1·34–2·91] per 1000 person-years) (Table 2). In both univariate and multivariate analyses (Table 2, supplementary Table 3–4), MSM had a lower risk of death compared to WSM (adjusted HR 0·49, 95% CI 0·32–0·76, p-value <0·001), and MSW (1·48 [1·20, 1·83], p-value <0·001) and men who inject drugs (1·72 [1·03, 2·85], p-value =0·038) had a higher risk of death compared to WSM and women who inject drug, respectively. After excluding 3736 participants who were diagnosed with AIDS at ART initiation, 22,673 patients were included in the analysis of progression from HIV to AIDS. The groups at higher risk of all-cause mortality were also at higher risk of disease progression.

3.3. Immunological and virological outcomes

61·7% of (16,294/26,409) patients had CD4+ cell count test results at 9–15 months after ART initiation, and 57·1% (15,093/26,409) had viral load test results at 6–18 months after ART initiation. CD4+ cell count response, CD4+/CD8 ratio normalization, and viral suppression were least common in men who inject drugs, followed by women who inject drugs and those infected through sex (Fig. 2.1). Rates of CD4+ cell count response and CD4+/CD8 ratio normalization were highest in WSM, and MSM had the highest rate of viral suppression. In multivariate analysis (Fig. 3, supplementary Tables 5, 8, 11), MSW (adjusted IRR 0·63, 95% CI 0·56–0·71, p-value <0·001), MSM (0·63 [0·55, 0·72], p-value <0·001), and male injection drug users (0·38 [0·21, 0·69], p-value =0·007) were less likely to achieve CD4+/CD8 ratio normalization compared to WSM and women who inject drugs, respectively. Men overall (0·95 [0·94, 0·97], p-value <0·001), MSW

Table 1
Baseline characteristics.

	Sexual route (n = 21,799)				Injection drug use (4610)			Overall			
	MSW (n = 8506)	WSM (n = 5118)	MSM (n = 8175)	p value	Women (n = 249)	Men (n = 4361)	p value	Women (n = 5367)	Men (n = 21,042)	p value	Overall (n = 26,409)
Age at enrollment											
Median (IQR)	40·71 [32·89, 51·43]	36·79 [29·78, 46·89]	30·28 [25·55, 37·18]	<0·001	36·96 [32·71, 41·96]	37·85 [33·55, 42·28]	0·070	36·80 [29·98, 46·39]	35·95 [29·24, 43·60]	<0·001	36·14 [29·40, 44·05]
16–30	1398 (16·44)	1311 (25·62)	3982 (48·71)		34 (13·65)	431 (9·88)		1345 (25·06)	5811 (27·62)	<0·001	7156 (27·10)
30–39	2670 (31·39)	1741 (34·02)	2768 (33·86)		126 (50·60)	2312 (53·02)		1867 (34·79)	7750 (36·83)		9617 (36·42)
40–49	1923 (22·61)	972 (18·99)	1055 (12·91)		80 (32·13)	1372 (31·46)		1052 (19·60)	4350 (20·67)		5402 (20·46)
≥50	2515 (29·57)	1094 (21·38)	370 (4·53)	<0·001	9 (3·61)	246 (5·64)	0·147	1103 (20·55)	3131 (14·88)		4234 (16·03)
Residence											
Rural	444 (5·22)	354 (6·92)	52 (0·64)	<0·001	10 (4·02)	339 (7·77)	0·040	364 (6·78)	835 (3·97)	<0·001	1199 (4·54)
Urban	8062 (94·78)	4764 (93·08)	8123 (99·36)		239 (95·98)	4022 (92·23)		5003 (93·22)	20,207 (96·03)		25,210 (95·46)
Marital status											
Married	5927 (69·68)	3691 (72·12)	1963 (24·01)	<0·001	106 (42·57)	2254 (51·69)	0·006	3797 (70·75)	10,144 (48·21)	<0·001	13,941 (52·79)
Not married	2530 (29·74)	1407 (27·49)	6202 (75·87)		140 (56·22)	2006 (46·00)		1547 (28·82)	10,738 (51·03)		12,285 (46·52)
Missing data	49 (0·58)	20 (0·39)	10 (0·12)		3 (1·20)	101 (2·32)		23 (0·43)	160 (0·76)		183 (0·69)
Baseline body mass index (BMI kg/m^2)											
<18	852 (10·02)	718 (14·03)	800 (9·79)	<0·001	32 (12·85)	365 (8·37)	<0·001	750 (13·97)	2017 (9·59)	<0·001	2767 (10·48)
18–24	4589 (53·95)	2569 (50·20)	5270 (64·46)		100 (40·16)	2347 (53·82)		2669 (49·73)	12,206 (58·01)		14,875 (56·33)
>24	1021 (12·00)	496 (9·69)	1097 (13·42)		18 (7·23)	192 (4·40)		514 (9·58)	2310 (10·98)		2824 (10·69)
Missing data	2044 (24·03)	1335 (26·08)	1008 (12·33)		99 (39·76)	1457 (33·41)		1434 (26·72)	4509 (21·43)		5943 (22·50)
Baseline hemoglobin (g/dl)											
Median (IQR)	13·50 [11·70, 14·90]	11·90 [10·40, 12·90]	14·80 [13·86, 15·60]	<0·001	11·80 [10·80, 12·90]	13·50 [11·90, 14·80]	<0·001	11·90 [10·40, 12·90]	14·20 [12·60, 15·20]	<0·001	13·70 [11·90, 15·00]
Anemia											
None	4429 (52·07)	2278 (44·51)	6765 (82·75)		108 (43·37)	2126 (48·75)		2386 (44·46)	13,320 (63·30)	<0·001	15,706 (59·47)
Mild	1928 (22·67)	1495 (29·21)	843 (10·31)	<0·001	86 (34·54)	1035 (23·73)	0·001	1581 (29·46)	3806 (18·09)		5387 (20·40)
Moderate to Severe	1545 (18·16)	957 (18·70)	328 (4·01)		31 (12·45)	621 (14·24)		988 (18·41)	2494 (11·85)		3482 (13·18)
Missing data	604 (7·0)	388 (7·58)	239 (2·92)		24 (9·64)	579 (13·28)		412 (7·68)	1422 (6·76)		1834 (6·94)
Time since HIV diagnosis (months)											
Median (IQR)	1·41 [0·66, 6·21]	1·97 [0·72, 13·37]	1·94 [0·69, 10·58]	<0·001	17·18 [3·78, 59·01]	11·07 [1·77, 44·81]	0·001	2·07 [0·72, 14·93]	2·10 [0·72, 13·14]	0·532	2·10 [0·72, 13·44]
≤6	6341 (74·55)	3340 (65·26)	5432 (66·45)	<0·001	82 (32·93)	1785 (40·93)	0·015	3422 (63·76)	13,558 (64·43)	0·094	16,980 (64·30)
>6	2165 (25·45)	1777 (34·72)	2743 (33·55)		167 (67·07)	2576 (59·07)		1944 (36·22)	7484 (35·57)		9428 (35·70)
Missing data	0 (0·00)	1 (0·02)	0 (0·00)					1 (0·02)	0 (0·00)		1 (0·00)
Baseline CD4+ cell count (cells per μL)											
Median (IQR)	172 [49, 279]	185 [69, 281]	252 [171, 334]	<0·001	210 [81, 283]	183 [81, 290]	0·522	185 [70, 281]	211 [98, 306]	<0·001	205 [92, 301]
>350	909 (10·69)	522 (10·20)	1661 (20·32)	<0·001	16 (6·43)	480 (1101)	<0·001	538 (10·02)	3050 (14·49)	<0·001	3588 (13·59)
201–350	2587 (30·41)	1692 (33·06)	3758 (45·97)		100 (40·16)	1398 (32·06)		1792 (33·39)	7743 (36·80)		9535 (36·11)
51–200	2555 (30·04)	1663 (32·49)	2071 (25·33)		71 (28·51)	1563 (35·84)		1734 (32·31)	6189 (29·41)		7923 (30·00)
≤50	2084 (24·50)	1022 (19·97)	628 (7·68)		36 (14·46)	773 (17·73)		1058 (19·71)	3485 (16·56)		4543 (17·20)
Missing data	371 (4·36)	219 (4·28)	57 (0·70)		26 (10·44)	147 (3·37)		245 (4·56)	575 (2·73)		820 (3·11)
Baseline CD4+/CD8 ratio											
Median (IQR)	0·19 [0·08, 0·31]	0·22 [0·11, 0·35]	0·26 [0·17, 0·37]	<0·001	0·24 [0·14, 0·34]	0·16 [0·08, 0·26]	<0·001	0·22 [0·11, 0·35]	0·22 [0·11, 0·33]	0·009	0·22 [0·11, 0·34]
<0.3	5327 (62·63)	2912 (56·90)	4541 (55·55)	<0·001	118 (47·39)	2322 (53·24)	<0·001	3030 (56·46)	12,190 (57·93)	<0·001	15,220 (57·63)
0·3–0·45	1228 (14·44)	873 (17·06)	2046 (25·03)		46 (18·47)	358 (8·21)		919 (17·12)	3632 (17·26)		4551 (17·23)
>0·45	739 (869)	609 (11·90)	1069 (13·08)		21 (8·43)	163 (3·74)		630 (11·74)	1971 (9·37)		2601 (9·85)
Missing data	1212 (14·25)	724 (14·15)	519 (6·35)		64 (25·70)	1518 (34·81)		788 (14·68)	3249 (15·44)		4037 (15·29)
WHO stage											
I or II	3262 (38·35)	2085 (40·74)	3822 (46·75)	<0·001	110 (44·18)	2108 (48·34)	0·326	2195 (40·90)	9192 (43·68)	<0·001	11,387 (43·12)
III or IV	5237 (61·57)	3027 (59·14)	4350 (53·21)		138 (55·42)	2219 (50·88)		3165 (58·97)	11,806 (56·11)		14,971 (56·69)
Missing data	7 (0·08)	6 (0·12)	3 (0·04)		1 (0·40)	34 (0·78)		7 (0·13)	44 (0·21)		51 (0·19)
Hepatitis B/C diagnosis	1147 (13·48)	585 (11·43)	987 (12·07)	<0·001	116 (46·59)	2271 (52·08)	0·005	701 (13·06)	4405 (20·93)	<0·001	5106 (19·33)
Missing data	2948 (34·66)	2055 (40·15)	1461 (17·87)		103 (41·37)	1793 (41·11)		2158 (40·21)	6202 (29·47)		8360 (31·66)
Tuberculosis diagnosis	630 (7·41)	235 (4·59)	151 (1·85)	<0·001	16 (6·43)	413 (9·47)	0·197	251 (4·68)	1194 (5·67)	0·010	1445 (5·47)

(*continued on next page*)

Table 1 (*Continued*)

	Sexual route (n = 21,799)				Injection drug use (4610)			Overall			
	MSW (n = 8506)	WSM (n = 5118)	MSM (n = 8175)	p value	Women (n = 249)	Men (n = 4361)	p value	Women (n = 5367)	Men (n = 21,042)	p value	Overall (n = 26,409)
Missing data	354 (4·16)	232 (4·53)	159 (1·94)		20 (8·03)	403 (9·24)					1168 (4·42)
ART initiation year											
2004–2011	1029 (12·10)	971 (18·97)	240 (2·94)	<0·001	53 (21·29)	1138 (26·09)	<0·001	1024 (19·08)	2407 (11·44)	<0·001	3431 (12·99)
2012–2013	1964 (23·09)	1379 (26·94)	1161 (14·20)		93 (37·35)	1137 (26·07)		1472 (27·43)	4262 (20·25)		5734 (21·71)
2014–2016	5513 (64·81)	2768 (54·08)	6774 (82·86)		103 (41·37)	2086 (47·83)		2871 (53·49)	14,373 (68·31)		17,244 (65·30)
Baseline ART regimen											
AZT+3TC+EFV/NVP	2422 (28·47)	1494 (29·19)	1620 (19·82)	<0·001	69 (27·71)	1210 (27·75)	0·642	1563 (29·12)	5252 (24·96)	<0·001	6815 (25·81)
D4T+3TC+EFV/NVP	1375 (16·17)	1154 (22·55)	364 (4·45)		59 (23·69)	1142 (26·19)		1213 (22·60)	2881 (13·69)		4094 (15·50)
TDF+3TC+EFV/NVP	4709 (55·36)	2470 (48·26)	6191 (75·73)		121 (48·59)	2009 (46·07)		2591 (48·28)	12,909 (61·35)		15,500 (58·69)

MSW=men who have sex with women. WSM=women who have sex with men. MSM=men who have sex with men. IQR=interquartile range. BMI= body mass index. WHO=world health organization. ART=antiretroviral therapy. AZT=zidovudine. 3TC=lamivudine. NVP=nevirapine. EFV=efavirenz. D4T=stavudine. TDF=tenofovir.

(0·94 [0·93, 0·96], p-value <0·001), and men who inject drugs (0·89 [0·81, 0·99], p-value =0·058) had a lower likelihood of CD4+ cell count response compared to women overall, WSM and women who inject drugs, respectively. Similarly, men overall (1·41 [1·25, 1·60], p-value <0·001), MSW (1·27 [1·09, 1·48], p-value =0·009), and men who inject drugs (1·81 [1·19, 2·76], p-value =0·020) were more likely to have HIV virological failure (viral load ≥400) compared with their female counterparts, whereas MSM (0·81 [0·67, 0·99], p-value =0·025) were less likely to have HIV viral load more than 400 after 12 months of ART initiation. Results did not vary when the cut-off value of HIV viral load for virological failure was 1000.

3.4. Adherence

MSM had the best adherence behaviors (i.e., receiving regular CD4 + cell counts and viral load monitoring, self-reported adherence to ART), while both men and women who inject drugs had the poorest (Fig. 2.2). In multivariate analyses (Fig. 3, supplementary Tables 6, 9, 12), compared with WSM, MSM were more likely to receive CD4+ cell counts monitoring (1·08 [1·07, 1·10], p-value <0·001) and viral load monitoring (1·13 [1·12, 1·15], p-value <0·001), but less likely to miss ART doses (0·54 [0·49, 0·61], p-value <0·001). Men overall had poorer self-reported adherence to ART compared to women overall (1·14 [1·06, 1·24], p-value =0·005). MSW and men who inject drugs had a slightly lower likelihood of receiving regular CD4+ cell counts monitoring than WSM (0·98 [0·97, 0·99], p-value <0·001) and women who inject drugs (0·92 [0·87, 0·97], p-value =0·011), respectively, but differences in regular viral load monitoring and self-reported adherence to ART were not significant.

3.5. ART side effects, ART interruption, and loss to follow-up

Overall, self-reported ART side effects were more frequent among women (0·83 [0·79, 0·87], p-value<0·001, supplementary Table 7, 10, 13) than men, which remained among individuals infected with HIV through sexual route (Fig. 2.3, Fig. 3). However, ART side effects were more commonly reported in men who inject drugs compared to women who inject drugs (1·78 [1·43, 2·22], p-value<0·001).

Overall, men were more likely than women to interrupt ART (1·47 [1·28, 1·70], p-value<0·001) and be lost to follow-up (1·78 [1·43, 2·22], p-value<0·001, Fig. 2.3, Fig. 2). Regarding individual HIV exposure groups, MSM had the lowest rates of ART interruption and loss to follow-up, followed by WSM, MSW, women who inject drugs, and men who inject drugs (Fig. 2.3). A higher percentage of PWID interrupted ART due to poor adherence compared to those infected through sex (supplementary Fig. 6). In multivariate analyses (Fig. 3), compared to WSM, MSW were more likely to be lost to follow-up (0·56 [0·49, 0·65], p-value<0·001) and men who inject drugs were more likely to stop ART (2·29 [1·50, 3·50], p-value=0·001). MSM were the least likely to be interrupt ART (0·34 [0·26, 0·44], p-value<0·001).

3.6. Sensitivity analyses

In sensitivity analyses, differences in clinical outcomes between MSM, MSW, and WSM, and between men and women who inject drugs were only significant during the first 24 months after initiating ART (Supplementary Table 1). Otherwise outcomes were similar with those reported above.

4. Discussion

In this retrospective cohort study of PLWHA receiving ART in China, we found that MSW had significantly higher risk of death, accelerated progression to AIDS, suboptimal immunological and virological responses, and were more likely to be lost to follow-up compared to WSM. MSM, however, had better survival, virological

Table 2
Association between risk group for HIV acquisition and time to death and progression from HIV to AIDS.

	Sexual contact			Injection drug use		Overall		Overall
	MSW	MSM	WSM	Men	Women	Men	Women	
Total follow-up (person-years)	19,342	13,923	13,804	10,505	646	43,770	14,450	58,220
Median follow-up (months, IQR)	24 (12–45)	15 (8–30)	33 (14–54)	29 (12–55)	31 (12–54)	21 (9–41)	33 (14–54)	22 (10–44)
All-cause deaths (n = 26,409)								
Number of events	326	28	134	468	15	822	149	971
Five-year cumulative mortality	3·83%	0·34%	2·62%	10·73%	6·02%	3·91%	2·78%	3.68%
Mortality per 1000 person-years (95% CI)	16·85 (15·07–18·79)	2·01 (1·34–2·91)	9·71 (8·13–11·50)	44·55 (40·60–48·77)	23·24 (13·01–38·33)	18·78 (17·52–20·11)	10·31 (8·72–12·11)	16.68 (15.65–17.76)
Unadjusted HR (95% CI), p value	1·65 (1·35, 2·02), <0·001	0·18 (0·12, 0·27), <0·001	..	1·92 (1·15, 3·19), 0·012	..	1·76 [1·47, 2·10], <0·001	..	..
Adjusted HR (95% CI), p value	1·48 (1·20, 1·83), <0·001	0·49 (0·32, 0·76), <0·001	..	1·72 (1·03, 2·85), 0·038	..	1·78 [1·49, 2·14], <0.001	..	..
Disease progression from HIV to AIDS (n = 22,673)								
Number of events	514	269	285	380	14	1163	299	1462
Total follow-up (person-years)	14,757	11,290	10,915	7821	547	33,868	11,462	45,330
Five-year cumulative incidence	7·29%	3·64%	6·58%	10·34%	6·31%	6·42%	6·57%	6.45%
Incidence rate per 1000 person-years (95% CI)	34·83 (31·89 - 37·98)	23·83 (21·06 - 26·85)	26·11 (23·17, 29·32)	48·59 (43·82, 53·73)	25·59 (13·99–42·94)	34·34 (32·39, 36·37)	26·09 (23·21, 29·22)	32.25 (30.62, 33.95)
Unadjusted HR (95% CI), p value	1·23 (1·06, 1·42), 0·006	0·71 (0·60, 0·84), <0·001	..	1·82 (1·06, 3·12), 0·029	..	1·16 [1·02, 1·32], 0·021	..	..
Adjusted HR (95% CI), p value	1·27 (1·09, 1·47), 0·002	0·83 (0·68, 1·00), 0·045	..	2·05 (1·18, 3·57), 0·011	..	1·16 [1·02, 1·33], 0·022	..	..

MSW=men who have sex with women. WSM=women who have sex with men. MSM=men who have sex with men. HR=hazard ratio. CI=confidence interval. IQR=interquartile range.

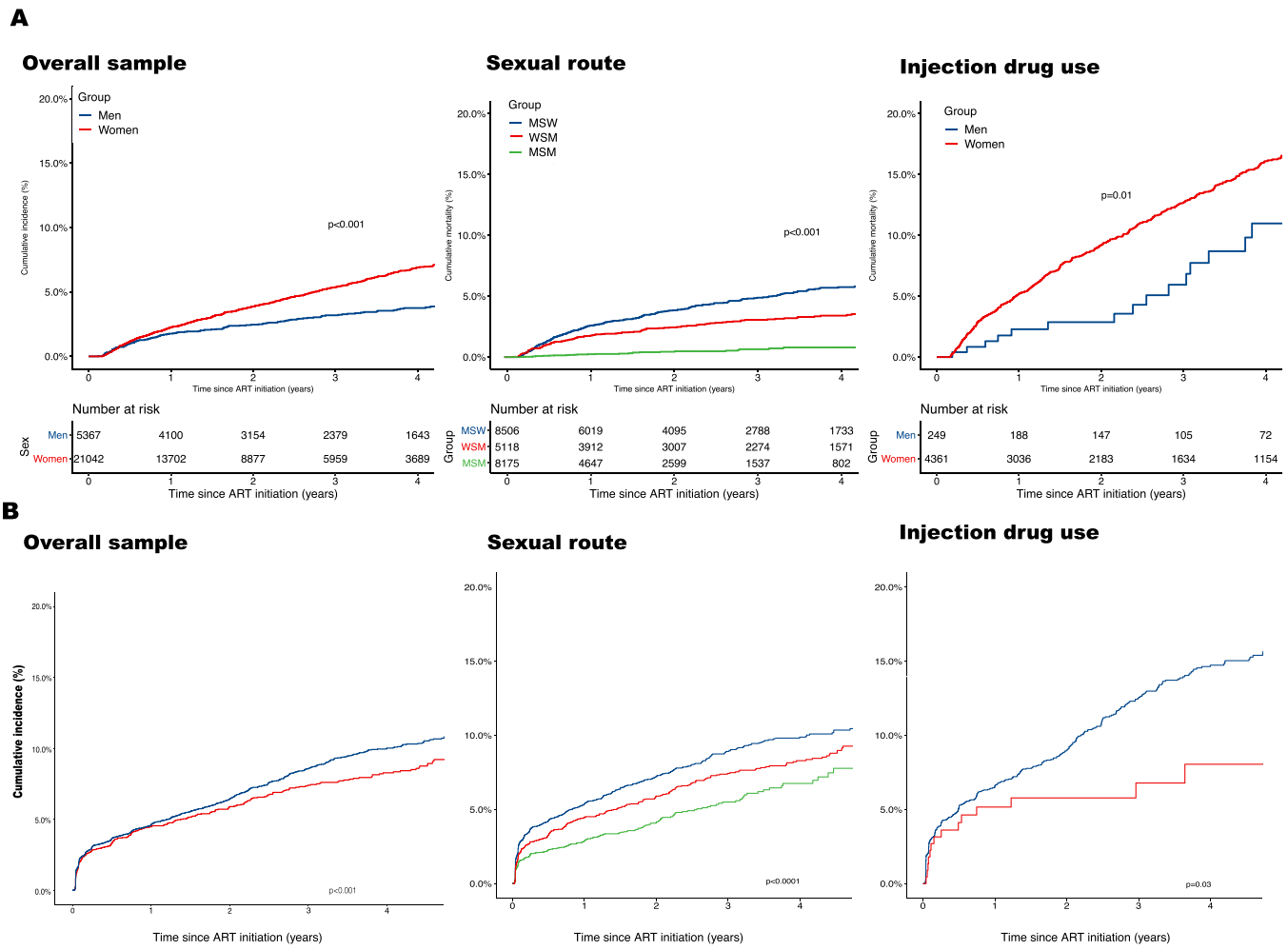

Fig. 1. All-cause mortality and disease progression from HIV to AIDS comparing men and women overall, MSW, MSM, and WSM, and men and women who inject drugs. Kaplan-Meier survival curves (A) and cumulative incidence curve of progression to AIDS (B)
MSW=men who have sex with women. WSM=women who have sex with men. MSM=men who have sex with men.

response, adherence behaviors, and retention in treatment compared to WSM. Men who inject drugs were almost twice more likely to die than women who inject drugs, experience disease progression to AIDS, virological failure, ART side effects, and interruptions in ART compared to women who inject drugs.

In general, HIV-infected men had higher risks of all-cause mortality, progression to AIDS, poorer immunological and virological failure, suboptimal ART adherence, and were less likely to be retained in care compared to women. Similar findings were reported in previous studies in China [15,16,27,28], other low-and middle-income countries [50–52], Europe [6,7], and three meta-analyses [4,5,53]. However, results from these studies based on men and women overall might be modified by a higher proportion of PWID in men [8,14,15]. Consistent with previous studies in China [15–18] and other countries [7,54], we noted that PWID had poorer treatment outcomes and ART adherence compared to people who acquired HIV through sex.

There are several reasons why men may have worse HIV treatment outcomes compared to women. Men have less access to HIV testing services compared to women because HIV testing through antenatal care and other sexual reproductive health services may not be available for men. Psychosocial factors such as masculinity and HIV-related stigma [55,56] might delay HIV diagnosis in men [52]. This is consistent with our finding that at ART initiation, MSW and men who inject drugs had more advanced immunosuppression compared to WSM and women who inject drugs, respectively. Tuberculosis [57] and chronic viral hepatitis coinfection [31], which have been associated with an increased risk of death among PLWHA, were also more common in MSW and men who injected drugs than women at ART initiation. It is also possible there are biological differences in pharmacokinetics and immune responses between men and women. Previous studies found that women tend to reach higher plasma concentration of antiretroviral drugs and have a higher degree of immune activation than men [58–61], and this might synergistically enhance the potency of ART. Indeed, we found that women were more likely to achieve CD4+/CD8 ratio normalization than men irrespective of HIV exposure groups. Sex differences in adherence behaviors might be another explanatory factor. Consistent with previous studies [62,63], we found that men had poorer ART adherence than women, but the overall sex difference in ART adherence disappeared when comparing between MSW and WSM and between men and women who inject drugs. This might be due to higher proportion of men than women in injection drug users, a population with poorer adherence to ART than other HIV exposure groups. In addition, MSW and men who inject drugs had poorer retention in treatment and were less likely to perform regular CD4+ cell count monitoring than WSM and women who inject drugs. Finally, higher mortality in men living with HIV might be attributable to men's higher risk of death from causes not related to HIV. In general population, men have higher rates of tobacco and alcohol use and violent deaths than women [50,64].

In contrast, we found that women overall tended to report more ART side effects than men overall, and this pattern persisted when

comparing WSM with MSW and MSM. This is in line with previous studies [65,66]. This could be due to sex differences in pharmacokinetics that women tend to have higher antiretroviral concentrations than men [58,61]. Besides, women's better ART adherence identified in this study could be another contributory factor. Sociocultural factors might also play a part. Specifically, given that in our study, adherence to ART was self-reported by patients, men might underreport their experiences of ART side effects for fear that this would undermine their masculinity [67]. In comparison, it is more socially approval and acceptable for women to explicitly exhibit their physical weakness or discomfort, so their threshold of reporting experiencing any side effect of ART might be lower than that of men. Additionally, even with better outcomes, we found that women have lower BMI and hemoglobin than men at ART initiation, which is in line with two previous studies in people living with HIV in China [27,28]. More studies are needed to investigate reasons underlying gender differences in BMI and hemoglobin in HIV-infected patients and whether such difference could affect treatment outcomes.

In our study, MSM had better survival and were more likely to achieve virological suppression than WSM. This is consistent with previous studies in China [21] and Europe [20]. However, one report from Brazil [19] reported that MSM have a higher risk of AIDS-related death than women even after adjusting for confounders. This may be because the follow-up duration for MSM in our study (median 1·23

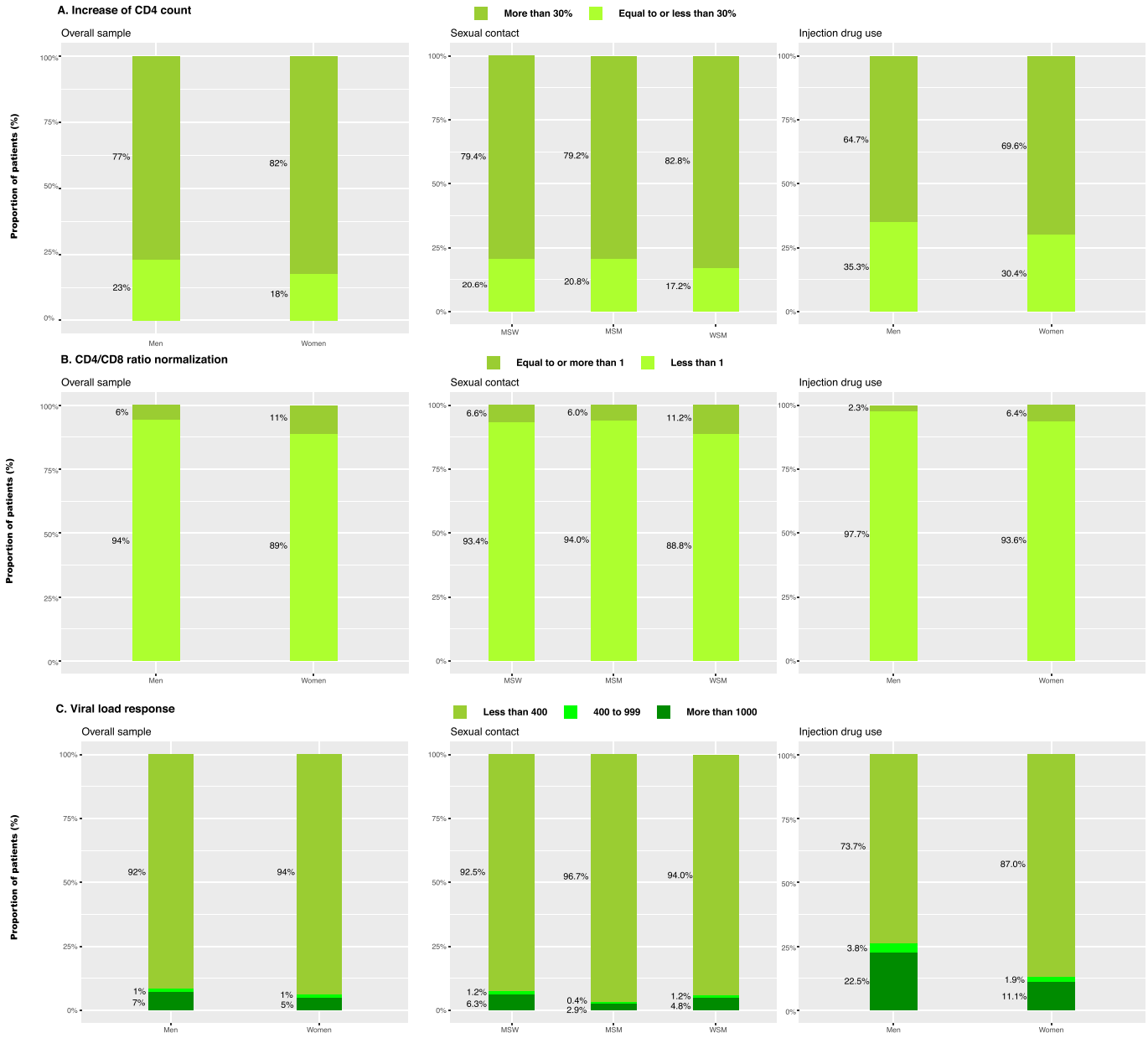

Fig. 2. Outcomes after ART initiation comparing men and women overall, MSW, MSM, and WSM, and men and women who inject drugs.

To illustrate repeated measurement outcomes using bar charts, we selected the median frequency of annual CD4+ cell count and HIV viral load testing; those without any missing ART dose throughout the follow-up were determined to have good ART adherence; the presence of any ART side effect and ART interruption throughout the follow-up were grouped under 'yes' respectively.

MSW=men who have sex with women. WSM=women who have sex with men. MSM=men who have sex with men.

Fig. 2.1 Immunological and virological response to ART.

Fig. 2.2 Regular CD4+ and HIV viral load testing and ART adherence.

Fig. 2.3 ART side effects and retention in treatment.

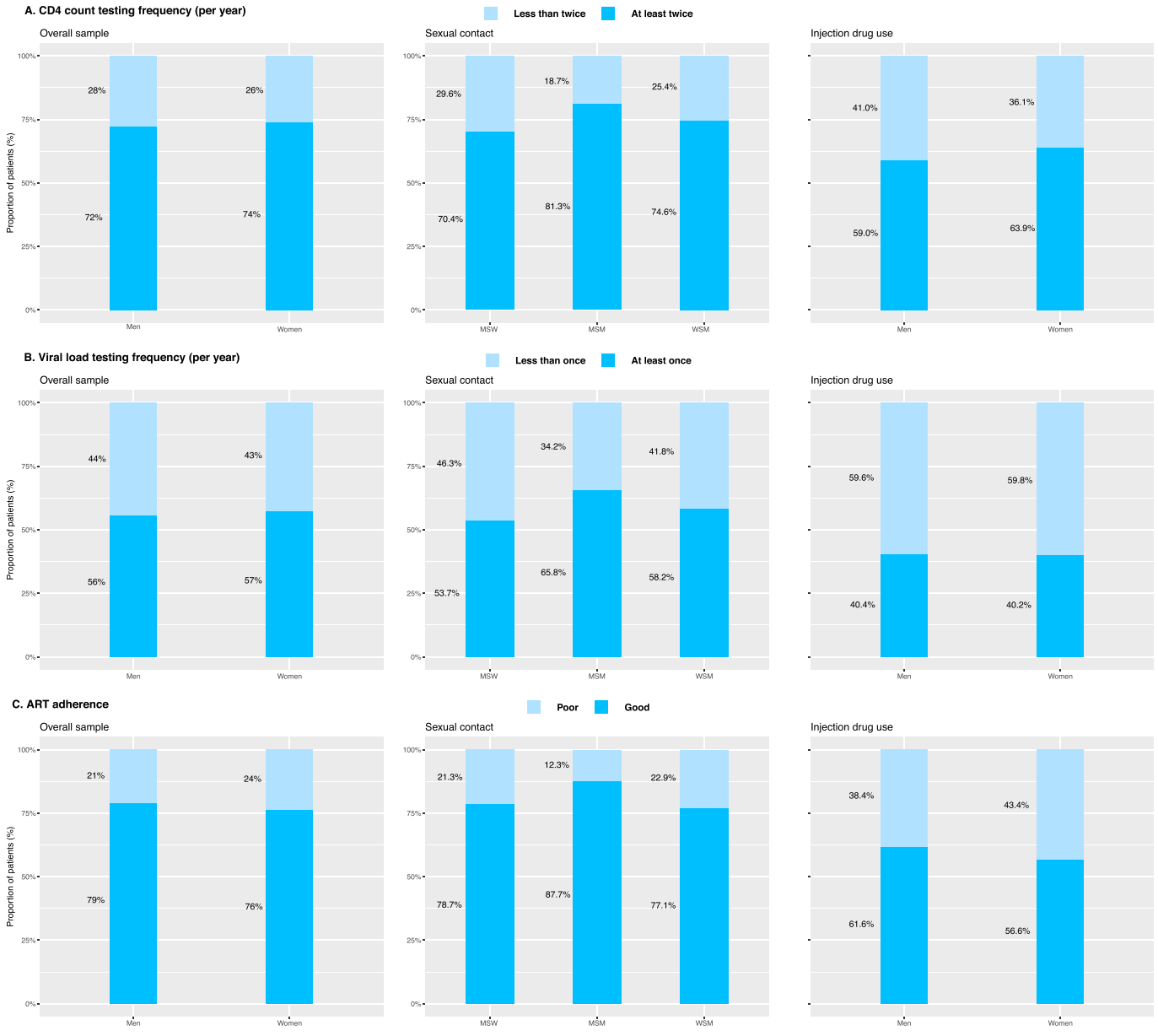

Fig. 2 Continued.

person-years [IQR 0·67–2·47]) is shorter than that in the Brazilian study (median 3·8 person-years [IQR 1·8–6·3]). Also, in that study from Brazil, the percentage of HIV-infected MSM who were not treated with ART was significantly higher than WSM were not on ART (21% vs 16%, *p*-value= 0·00,021) [19], whereas all the participants in our study were started on a standard first-line ART regimen. Another possible reason is that the age of MSM in our study (median 30·3 IQR [25·5–37·2]) was relatively younger than that in the Brazilian study (median 34·1 IQR [27·4–41·3]) [19]. We found that MSM had lower risk of progression to AIDS than WSM. This is in contrast to a study conducted in Jiangsu Province, China, in which MSM showed faster progression to AIDS compared with patients infected through other routes [22]. However, the length of follow-up for MSM in that study was not reported; results from that study were simply based on univariate analysis that did not adjust for confounders, and a proportion of participants in that study were not treated with ART [22]. In our study, nearly all MSM (99·36%) lived in cities, and most of them (71·25%) were from Guangzhou and Shenzhen, two first-tier cities with high annual median income [68]. Economic and sociocultural factors might therefore impact health outcomes among MSM.

Behavioral factors might explain the favorable treatment outcomes among MSM in our study. MSM were more likely to perform routine CD4+ cell count and viral load monitoring, be adherent to ART, and be retained in treatment than WSM. These behaviors have been associated with prolonged survival in people living with HIV [17,21,34,69,70]. HIV prevention campaigns targeting MSM in China in recent years might have led to increased perceived risk, earlier HIV-testing, and improved adherence behaviors [21]. MSM in our study were younger and their immune status were less-compromised at ART initiation. Increasing acceptance of male homosexuality in China [71] might also contribute to a supportive healthcare environment which ensure the high utilization of medical services in MSM with HIV [72,73]. Lastly, more than two thirds of MSM in our study initiated ART after 2014 when the threshold for ART initiation has lowered, and were treated with a more efficacious tenofovir-based regimen.

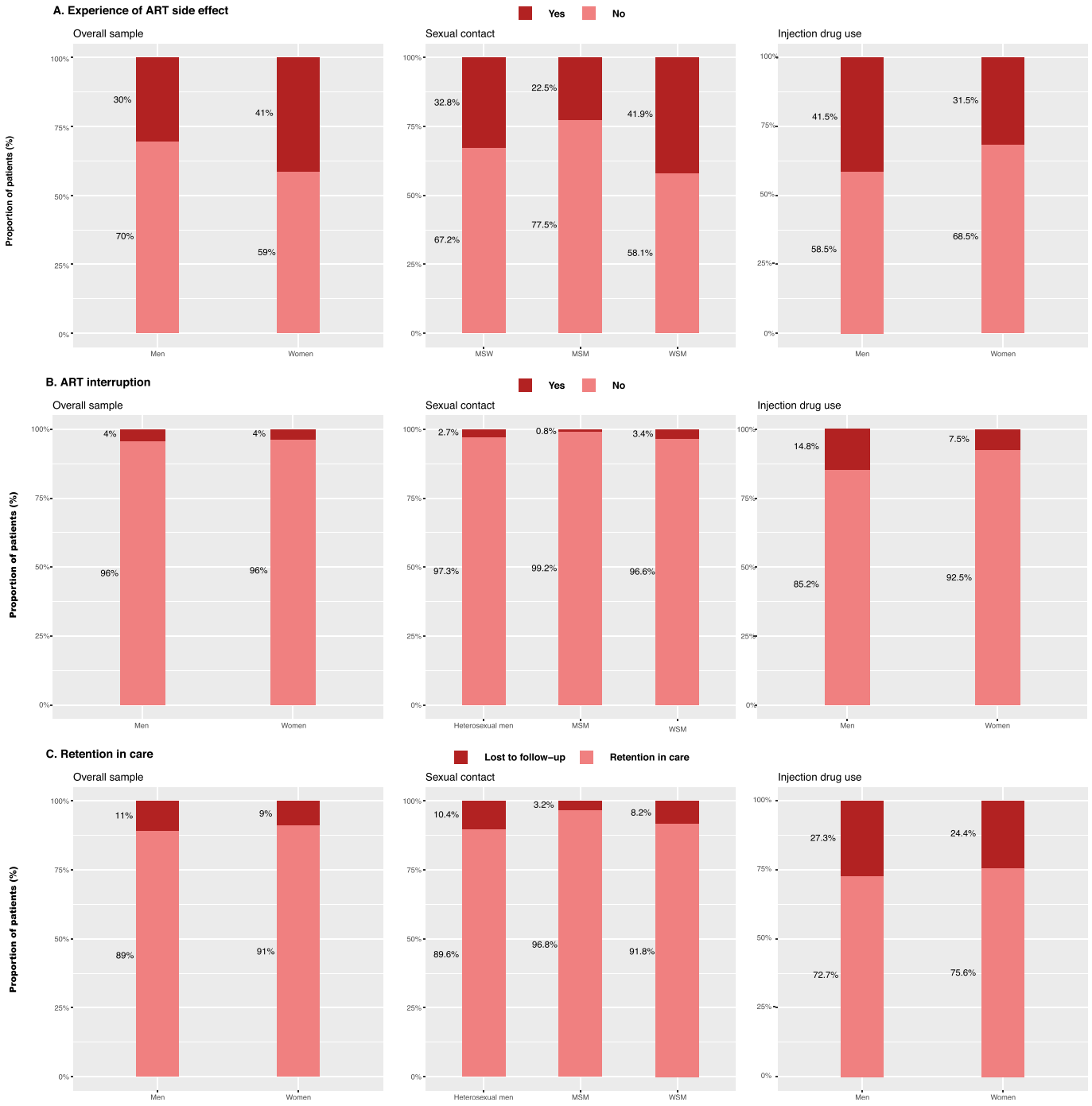

Fig. 2 Continued.

We found that men who inject drugs had worse treatment outcomes compared to women who inject drugs. This difference was larger than that between MSW and WSM. Contrary to the results comparing between MSW and WSM, men who inject drugs were also more likely to report ART side effects than their female counterparts. This may be because men tend to have heavy drug use and poly-drug use [74–76], leading to and more frequent ART side effects resulting from drug interactions between ART and medications to treat substance use [77]. Frequent ART side effects in men who inject drugs might partly lead to poor ART adherence, and this might partly account for their more frequent ART interruption compared to women who inject drugs.

Our study has several limitations. First, HIV exposure groups was self-reported, so patients with one type of HIV exposure groups (e.g., MSM) might simultaneously engaged in other high-risk behaviors (e.g., injection drug use). We attempted to limit the potential of misclassifying patients by excluding those who had both a history of methadone use and self-reported sexual exposure to HIV. Second, because of the limited information for causes of death, we were unable to differentiate between AIDS-related and non-AIDS-related deaths which might differentially affect men and women. Third, we were unable to control for other known and unknown confounding factors, such as income, educational level, smoking, alcohol use, ages at sexual debut, and high-risk sexual behavior due to the lack of relevant information in the database. Due to the same reason, we were unable to differentiate general MSM from transgender women whose treatment outcomes of ART might be different. Fourth, patients who

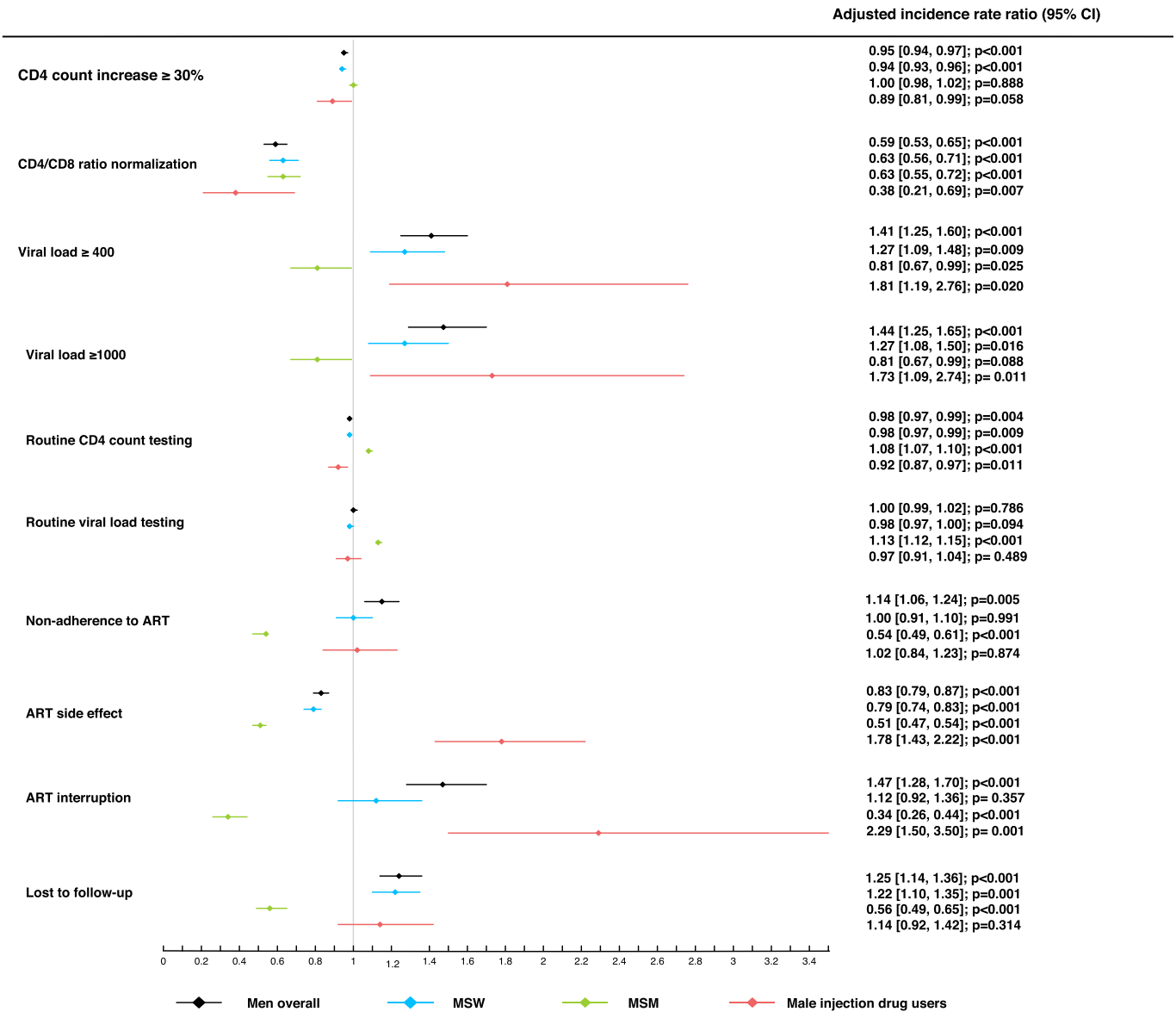

Fig. 3. Adjusted associations between all outcomes comparing men and women overall, MSW, MSM, and WSM, and men and women who inject drugs. Reference groups were women overall, women infected through sex and women who inject drugs respectively. MSW=men who have sex with women. WSM=women who have sex with men. MSM=men who have sex with men.

were lost to follow-up were not linked to death registries, therefore mortality may be underestimated. Fifth, the small number of women infected through injection drug use (n = 249, 5·4%) limited the statistical power of our analysis. Sixth, the follow-up duration of MSM in our study was relatively short, which might not be long enough to observe adverse outcomes. Finally, we used a non-probabilistic sample and the vast majority (95%) of participants were from urban areas, limiting the generalizability of our results to other regions. Additional studies from China and other countries with large cohorts and higher proportion of HIV-infected patients from rural areas and female injection users are needed.

To the best of our knowledge, this is the first cohort study to comprehensively investigate differences in survival, disease progression, immunological and virological responses, and adherence behaviors among MSW, MSM and WSM, and between men and women who inject drugs. Our findings highlight the importance of identifying potentially at-risk MSW (e.g., old male living in rural areas, male migrant workers, and male sex workers) and promoting HIV health education and HIV testing services among them. Since sex is the primary route of HIV transmission in China, delayed HIV diagnosis in MSW not only results in poorer treatment outcomes but also puts their sexual partners at an increased risk of HIV infection. There is also a need for further research to investigate tuberculosis and chronic viral hepatitis coinfection among MSW living with HIV. Our findings in MSM are somewhat reassuring. Nonetheless, the follow-up time for MSM in this study was relatively short and the majority of them lived in cities, warranting additional studies with a longer follow-up and a larger proportion of MSM from rural areas to assess the long-term treatment outcomes and adherence in this population. Notably, the prevalent high-risk sexual behavior among MSM, especially among those with earlier sexual debut, could increase the risk of HIV transmission to their HIV-negative sexual partners [78–80]. It is therefore crucial to incorporate promotion regarding protected sexual behaviors into standardized follow-up among this population [78]. Particular attention is needed among men who inject drugs to improve timely HIV diagnosis and linkage to HIV care, clinical management of substance use disorder, treatment for HBV or HCV coinfection, drug interactions, and retention in treatment.

Declaration of Competing Interest

We declare no competing interests.

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Contributors

HZ and LL had the idea for the study. LL, TY and HZ designed the protocol, LL, TY and HZ wrote the manuscript. JW provided consultation on data analysis. TF and WC contributed to manuscript preparation and language editing. PL, XT, GX, DC, and BL critically reviewed the manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100351.

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