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Factors of HIV Virologic Failure And Drug Resistance In Chinese Patients After 48 Months Of Antiretroviral Treatment, 2008-2012

By

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Degree to be awarded: MPH

Epidemiology

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Factors of HIV Virologic Failure And Drug Resistance In Chinese Patients After 48 Months Of Antiretroviral Treatment, 2008-2012

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An abstract of
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Abstract

Factors of HIV Virologic Failure And Drug Resistance In Chinese Patients After 48 Months Of Antiretroviral Treatment, 2008-2012

By Wei Kan

Objective: To explore factors associated with HIV virologic failure and drug resistance among HIV-positive Chinese patients four years after initiating first-line 3TC-based antiretroviral treatment (ART) in 2008 at five sentinel sites.
Design: First-line ART initiators who were previously treatment naïve were selected using consecutive ID numbers from the 2008 National Surveillance Database into a prospective cohort study. Questionnaires and Blood samples were collected in 2011 and 2012 to assess the outcomes of interest: virologic failure and HIV drug resistance (HIVDR). Questionnaires and data from National Surveillance Database assessed demographics and drug adherence data.
Results: 536 eligible patients were retained in the study, the 48-month risk for VF was 63(11.8%) and DR was 27(5.0%). 41(7.6%) participants had viral load ≥ 1000 copies/ml in 2011 and 49 (9.1%) participants had viral load ≥ 1000 copies/ml in 2012. 21(3.9%) participants were found to HIVDR 2011, 27 (5.0%) participants were found to have HIVDR in 2012. There were no statistical differences in virological outcomes and drug resistance in 2011 and 2012. Female participants initiated with D4T based regimen were more susceptible to both virological failure (aOR=2.5 95% CI: 1-6.1 P-value=0.04) and HIVDR (aOR=3.6 95% CI: 1-12.6 P-value=0.05), interestingly, male participants showed no such trait (Crude OR=0.6 95% CI: 0.3-1.4 P-value=0.24). 472 (88.1%) participants reported not missing a dose in the past month at the time of survey. Male participants missing doses in past month were more susceptible to both virological failure (aOR=2.8 95% CI: 1.1-7 P-value=0.03) and HIVDR (aOR=9.7 95% CI: 2.1-44.1 P-value<0.01). All 27 participants detected with HIVDR had NNRTI mutations, 21 (77.8%) had NRTI mutations; no protease inhibitor mutations were detected.
Conclusions: Our findings suggested considerably successful treatment outcomes. We found in the study that female participants initiated with D4T based regimens were more vulnerable to virological failure and HIVDR, while male participants had a higher tendency to have challenges with drug adherence.

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Running head: Virologic failure and drug resistance among HIV+ Chinese ART patients

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Introduction

Antiretroviral treatment (ART) has dramatically improved health outcomes and decreased HIV-associated morbidity and mortality through virologic suppression and subsequent CD4 recovery. (1-4)In 2003, China launched a National Free Antiretroviral Treatment Program (NFATP) that includes life-long provision of free ART for people living with HIV who meet the national treatment criteria.(5, 6) The national treatment criteria in 2008 were: (1) CD4 cell count $\leqslant 200/mm^3$; (2) World Health Organization (WHO) stage III/IV diseases, or (3) willingness to receive ART, regardless of the criteria 1 and 2.(7)

The State Council AIDS Working Committee Office and the United Nations Theme Group on AIDS estimated that there were more than 700,000 persons living with HIV in China in 2008, and more than 52,000 patients across 31 provinces, autonomous regions, and municipalities had received ART (made freely available by the NAFTP) by Aug 2008.(8)

With the rapid scale-up of treatment and challenges with adherence, virologic failure(VF) and HIV drug resistance (HIVDR) are ever present and mounting concerns. Incomplete virologic suppression, a major cause of HIVDR, not only compromises therapeutic efficacy for the individual receiving treatment, increasing the risk of viral rebound and opportunistic infections, but also increases the risk of transmitting drug resistant strains to other individuals in the general population.(9) (10, 11)

Observational studies in China have documented the prevalence of virological failure and HIVDR strains among treated individuals living with HIV. A cross-sectional study conducted in Yunnan, Guangxi and Xinjiang provinces in 2010 stated that one-year HIVDR prevention and drug resistance prevalence was 75.3% and 4.1%(5). VF prevalence for sexual transmitted

population and intravenous drug users(IDUs) were 8.3% and 19.3%, separately. A 6-year follow-up study ended in 2010 suggested an incidence of 14.1 per 100 person-year for virological failure and 11.9 per 100 person-year for drug resistance among former plasma donors in Anhui Province.(12)

NFATP recommended to switch the first-line regimen from Didanosine (DDI) to Lamivudine (3TC) in 2008, there are few nationwide, prospective studies in China reporting predictors of virological failure and drug resistance for people live with HIV after initiating 3TC based regimens, to the extension of our knowledge, this is the first long-term study evaluate VF and HIVDR on 3TC based regimen. The aim of this study is to evaluate predictors of HIVDR and virological failure occurring in a prospective cohort of Chinese HIV patients four years after first initiating first-line 3TC-based ART in 2008 at five sentinel sites. We stratified our analyses by gender based on conflicting findings on gender differences both in virological responses and drug resistance to different ART regimen as well as gender differences in ART adherence.(13-16)

Ethics Statement

The study was approved by the institutional review board (IRB) of the National Center for AIDS/STD Control and Prevention of the China Center for Disease Control Prevention (NCAIDS, China CDC). All participants provided written informed consent before participation.

Study Design and Data Collection

This study was designed under the WHO Surveillance of HIV drug resistance in adults receiving ART for 48 months. (10, 17, 18)

In 2011, five provinces in China were selected to conduct a prospective cohort study with a follow-up study at 12 months: Guangxi, Henan, Hubei, Xinjiang and Yunnan. Patients were sampled from the National HIV Surveillance Database. Participant eligibility criteria included being age ≥ 18 years; having initiated NAFTP-sponsored first-line ART in 2008; having been on ART for 36±6 months in 2011; and providing consent to participate in the study.

Data collection involved questionnaires administered by trained study personnel using structured interviews. Demographic and self-reported adherence data were collected. Additional HIV-specific data including route of transmission, initial ART regimen, latest ART regimen, ART distribution location, adverse effects, and CD4 cell count at 2008 were collected from the National HIV Surveillance Database.

Laboratory analysis

Blood specimens were collected from all participants to test CD4 cell count, HIV-1 RNA viral load (VL), and HIV-1 drug resistance mutations during the time of the 2011 and 2012 surveys. Plasma was isolated and stored at -80°C at a provincial CDC laboratory and then transferred to NCAIDS. CD4 cell count estimation was conducted at CDC laboratories using flow cytometry (FACSC Calibur, BD Company, USA) within 24 hours after specimen collection.

Plasma HIV RNA was quantified with real-time NASBA (NucliSense Easy Q, bioMerieux, France) or COBAS (Roche Applied Biosystems, Germany) according to manufacturer recommendations using in-house PCR (polymerase chain reaction).(19) Virologic failure was defined as VL ≥1000 copies/ml. According WHO protocol, (20) HIV drug resistance tests were performed on samples with VL ≥1000 copies/ml. HIV-1 *pol* gene (protease 1-99 amino acids and part of reverse transcriptase 1-252 amino acids) were amplified, purified and analyzed using the

Stanford HIV Drug Resistance Database (http://hivdb.stanford.edu/). Any low-, intermediate-, or high-level resistance identified was defined as HIVDR.(21-24) HIV VL and drug resistance mutation testing was conducted at NCAIDS.

Data analysis

Questionnaire data were double-entered using Epidata 3.1 (The Epidata Association Odense, Denmark). Statistical Analysis System (SAS 9.4, SAS Institute Inc., Cary, NC, USA) was then used for data cleaning and analyses.

48-month risk for the outcomes of interest was calculated as the proportion of unique persons who had experienced VF or HIVDR by the end of follow-up in 2012.

Covariates of interest were described using counts and percentages overall and by the outcome of interest, stratified by gender. Univariate logistic regression models were constructed to explore associations between covariates of interest and virological failure or HIVDR. Odds ratios (OR) and 95% confidence intervals (CIs) are reported. Variables that were significant ($P < 0.05$) in the univariate models were then fit into multivariate logistic regression models assessment for/removal of collinear variables that had the weakest association with the outcome. Adjusted ORs (aOR) and 95% CIs were presented. $P < 0.05$ was defined as statistically significant, and all tests were two sided. Descriptive analysis on DR mutation results was conducted among 27 HIVDR participants.

Results

1100 subjects were selected using consecutive ID numbers from 2008 National Surveillance Database; of those, 490 were lost follow-up by December, 2012. Among those lost to follow up,

139 died, 55 emigrated, 134 lost contact, 17 refused to participate, 65 stopped ART before 30 months, 36 transferred, 8 were under custody, 6 failed to provide a blood sample, 3 switched from ART to Tangcao tablet (an antiviral Chinese herbal therapy), 2 became pregnant and switched to other regimens and 1 was paralyzed. After excluding 74 participants for failing the eligibility criteria, 536 participants were included in the final 24-month analysis (Figure 1). The 48-month risk of virological failure was 11.8% and risk of drug resistance was 5%.

Demographic and ART Information (Tables 1-2)

Of the 536 eligible participants, 51.8% were male; 76.49% were Han majority; 45.0% had an education level of elementary school or less; 56.2% were farmers; and 10.6% were unemployed with the rest having regular income.

All regimens in this cohort were 3TC-based. Initiated Nucleoside Reverse Transcriptase Inhibitors (NRTI) regimens included Zidovudine (AZT) (n=349, 65.1%) or Stavudine (D4T) (n=187, 34.9%). Sixty-six (12.3%) participants later changed to TDF based regimen. Initiated Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) regimens included Nevirapine (NVP) (n=421, 78.5%) or Etravirine (EFV) (n=115, 21.5%). Fifty-five (10.3%) participants later changed to LPV/r based regimen. 169 (31.5%) participants switched the initial ART regimen during 2008-2012, but no statistical significant difference was found in VF and HIVDR risk between participants who switched regimens and participants who did not switch regimens.

We found that 38.4% participants were hesitant to accept ART in the future, 36.8% participants reported doubts whether ART was health promoting and 42.5% participants did not report that poor ART adherence necessarily contributed to HIVDR. Additionally, 40.5% of

participants were not always satisfied with support from friends or relatives. 472 (88.1%) participants reported not missing a dose in the month prior to the date of the survey.

Multivariate model results (Table 3)

As shown in Table 3, minority male participants were at higher risk for both virological failure (aOR=2.9 95% CI: 1.1-7.3 P-value=0.02) and HIVDR (aOR=12.2 95% CI: 1.8-84.8 P-value=0.01) compared to Han majority male participants, while female minorities were only at a higher risk for HIVDR (aOR=4.8 95% CI: 1.2-19.7 P-value=0.03).

Female participants initiating D4T-based regimens were at a higher risk for both virological failure (aOR=2.5 95% CI: 1-6.1 P-value=0.04) and HIVDR (aOR=3.6 95% CI: 1-12.6 P-value=0.05) versus those initiating an AZT-based regimen; interestingly, different from their female counterparts, male participants showed no such association (OR=0.6 95% CI: 0.3-1.4 P-value=0.24). Also, female participants had a higher risk of virological failure given adverse side-effects (aOR=2.7 P-value=0.03). Male participants with missed doses in the month prior to the survey were at a higher risk of both virological failure (aOR=2.8 95% CI: 1.1-7 P-value=0.03) and HIVDR (aOR=9.7 95% CI: 2.1-44.1 P-value<0.01) versus those without missed doses in the preceding month. Conversely, missed doses in prior month was not significantly associated with virological failure or HIVDR for women.

HIV Drug Resistance and Subtype (Table 4)

Drug resistance identified in our study was consistence with the NFATP recommended ART regimen. All 27 participants detected with drug resistance had NNRTI mutations, 21

(77.8%) had NRTI mutations. The dominant subtype was CRF07_BC for both males (61.5%) and females (50%). All participants found with DR had developed DR towards NNRT; 85.7% male participants and 69.2% female developed DR toward NRTI; no Protease Inhibitor mutation was detected. There were no CRF08_BC subtypes detected in the study population.

Discussion

The 48-month risk of virological failure was 11.8% and HIVDR was 5.0%, which indicated a considerably good treatment outcome given meta-analysis suggested a 37-48 months HIVDR prevalence ranging from 6.4%-47.92% in China,(9) one-year VF and DR incidence in 2009 were 3.5%.(25) This study substantiates the finding that VF and DR largely decreased since the wide-spread of 3TC-based regimens.(26) Studies showed mixed findings of gender differences on ART adherence and treatment outcomes. (14, 16, 27, 28) In this study, we found male participants had slightly higher risk of virological failure (12.2% versus 11.2%, P-value = 0.72) but lower risk of HIVDR (2.4% versus 5.4%, P-value= 0.69) than women. Women had a lower chance of both VF and DR when reported missing doses in the past month, possibly suggesting women had better drug adherence similar to two other studies done in China. (29, 30)

Mitochondrial toxicity caused by D4T had been reported to cause many adverse effects such as lactic acidosis, lipodystrophy, and peripheral neuropathy. (31, 32) Following the WHO recommendation,(33) the NFATP advocated switching the first-line regimen from D4T to TDF in 2012. The percentage of people living with HIV initiating D4T-based regimen changed from 34.3% in 2010, around 10% in 2012 and 0.9% in 2014;(34) however, there were still 29.9% participants in our study who stayed on D4T-based regimens in 2012. We found in this study that women, not men, who initiated D4T-based regimens were more susceptible to virological failure

(women vs. men OR=2.3 95% CI: 1.0-5.7 P-value= 0.06) and drug resistance (women vs. men OR=3.0 95% CI: 0.8-11.3 P-value=0.11), consistent with previous findings that D4T was more likely to increase the risk of mitochondrial toxicity in women. (35, 36) It was noteworthy that we did not see a statistical difference in VF (OR=1.4 95% CI: 0.4-4.2 P-value=0.60) and DR (OR=1.0 95% CI: 0.2-4.2 P-value=0.98) between women who initiated and remained on D4T-based regimens and those who switched to AZT/TDF based regimens. It is a possible that women switched regimens because of VF; however, further studies need to be done to explore when to switch ART regimen for women receiving D4T-based regimens. It is important to mention that data on ART adherence and adverse effects were collected in 2012, when there were only four female participants still using D4T-based regimens who experienced virological failure. The sample size was not sufficient enough to explore whether D4T-based regimens affect drug adherence and adverse effects for women.

Drug adherence and adverse effects influenced our outcomes differently for men compared to women, despite their evenly distribution across gender. Male participants were at higher risk of both VF and DR if they reported missed doses. More detailed studies need to be done in the amount and frequency of missing treatment. However, female participants showed a higher risk of virological failure if they had adverse effect compared to male participants. This calls for further researches of what types adverse effects and how they affect ART adherence and virological outcome across gender.

Another interesting finding on ART adherence was that frequency of drug taken reminded by friends and family yielded opposite results from those individuals being reminded by doctors. Although the results were not statically significant, it is interesting to note that participants with

worse treatment outcomes were more frequently reminded by doctors, while participants with better outcomes were more frequently reminded by friends or family. A possible explanation is that doctors were more concerned about participants who experienced virological failure. Also, though we did not find any statistical association between willingness of participants to accept ART and VF or DR, our study recommended that further psychological and behavioral interventions are needed.

We noticed in our study, 61.5% DR in male participants were IDU transmitted, yet there were only 4(6.3%) male IDU participants above 45 years old. In addition, we found that younger (<45 years old) IDU population were more likely to miss doses (18.64%) compared to heterosexually transmitted population (8.75%) and blood transmitted population (12.12%). This finding was consistent with studies that implied younger males were at a higher risk of drug abuse and unprotected sexual behaviors.(37, 38) Caution is needed when interpreting the study results from multivariate model that older age (>45) served as a protective factor for DR in men. A previous study in HIV positive IDU population in China suggested that there is no association between VF and sex or age.(39) Once we removed IDU population, there was no statistical significant difference between DR and age. This result indicated that younger IDU population could be a main source of VF and DR; therefore they could be future targeted population for behavioral intervention.

The influence of ethnicity towards DR in the study was similar across gender; minorities had a higher risk for both VF and DR. It was frequently reported that minorities tend to have lower social economic status than Han majorities, followed by lower education level and fewer access to health facilities.(40) Many studies also reported that the percentage of high risk

population for HIV transmission such as female sex workers (FSWs) and IDUs were higher in minorities than in Han majority. (41-43) In addition, it is difficult for health professionals to reach for some minorities because of their geographic locations. While it is important to advocating for policy changes,(44)there're still needs to emphasis behavior interventions among this population given a meta-analysis of ART adherence in China mentioned that the percentage of having adequate ART adherence among FSW and IDU population was lower in China than other low- and mid-income settings(45).

The findings of CD4 cell count was consistent with those of virological failure, where lower CD4 cell count indicated a higher risk of VF and DR. NFATP changed treatment criteria from CD4 cell count$\leqslant$200/mm^3 to CD4 cell count$\leqslant$350/mm^3 following the WHO suggestion in 2011,(7, 17, 46) the study indicated that male participants initiated treatment at CD4 cell count$\leqslant$ 350/mm^3 were still at higher risk towards VF (aOR=7.1 95% CI: 1.1-45.8 P-value=0.04).

Among participants infected by blood transmission, we only found HIVDR subtype B; only one subtype C was found in participants infected with IDU, the dominant subtype was CRF07_BC, found both in participants infected by heterosexual transmission and IDU. The most common NNRTI mutation sites were K103N (40.7%), K101E (22.2%) and V108I (22.2%); the most common NRTI mutation sites were M184V (81.0 %) and K70R (19%). Interestingly, compared to a one-year follow-up study in China with all participants initiated ART in 2011,(47) there is no V108I in their study and we did not find K65R in our study.

Study findings should be interpreted in light of several limitations. Though we did not account for transmitted drug resistance in this study, given previous studies implied a low transmitted drug resistance (<5%) during this time period (48-50) in China, we could be

relatively certain that participants were outcome free in 2008 as they were new ART initiators. Another limitation of our study is that the outcomes were measured only in 2011 and 2012, and thus we may be underestimating outcome risk. Also, route of transmission was collected in 2008 when assessing HIV infection among men who have sex with men was not part of data collection instruments. Roughly half of the study participants selected for possible inclusion in the study for having initiated first-line ART in 2008 were lost to follow-up by 2012, creating a possible selection bias, possibly for individuals with better ART adherence. The potential DR in our study is 39.7% based on WHO definition of potential DR. There were 36 participants who experience VF but did not have a DR outcome, of 1,110 subjects, by eliminating deaths and transfer outs, 36.6% can be classified as possible HIVDR.(51) Misclassification of self-reported data is possible, though we do not expect this misclassification to be differential by the outcome of interest and thus any such information bias would bias our results toward the null.

Conclusions

This study advocated to increase treatment baseline to CD4 cell count to $<500/mm^3$ following the WHO recommendation in 2013.(52) Additionally, we suggest supplemental studies on whether and when to change ART regimen for women initiated with D4T-based regimen. Finally, this study indicated minorities and younger men who become infected through IDU may be groups to strategically focus counseling and increased adherence support programs.

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Transparency Delcarations

Vincent C. Marconi has received fees from ViiV Healthcare.

References

1. Hong SY, Nachega JB, Kelley K, Bertagnolio S, Marconi VC, Jordan MR. The global status of HIV drug resistance: clinical and public-health approaches for detection, treatment and prevention. Infectious disorders drug targets 2011;11(2):124-33.

2. Gabillard D, Lewden C, Ndoye I, Moh R, Segeral O, Tonwe-Gold B, Etard JF, Pagnaroat M, Fournier-Nicolle I, Eholie S, Konate I, Minga A, Mpoudi-Ngole E, Koulla-Shiro S, Zannou DM, Anglaret X, Laurent C, Group AMMS. Mortality, AIDS-morbidity, and loss to follow-up by current CD4 cell count among HIV-1-infected adults receiving antiretroviral therapy in Africa and Asia: data from the ANRS 12222 collaboration. *Journal of acquired immune deficiency syndromes* 2013;62(5):555-61.

3. Montaner JS, Lima VD, Harrigan PR, Lourenco L, Yip B, Nosyk B, Wood E, Kerr T, Shannon K, Moore D, Hogg RS, Barrios R, Gilbert M, Krajden M, Gustafson R, Daly P, Kendall P. Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission: the "HIV Treatment as Prevention" experience in a Canadian setting. *PloS one* 2014;9(2):e87872.

4. Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J, Stryker R, Johnson P, Labriola DF, Farina D, Manion DJ, Ruiz NM. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *The New England journal of medicine* 1999;341(25):1865-73.

5. Wang X, Yang L, Li H, Zuo L, Liang S, Liu W, Dong Y, Yang S, Shang H, Li J, Kang L, Zhong P, Zheng W, Liao L, Xing H, Chen RY, Ruan Y, Shao Y. Factors associated with

HIV virologic failure among patients on HAART for one year at three sentinel surveillance sites in China. *Current HIV research* 2011;9(2):103-11.

6. Zhang F, Dou Z, Ma Y, Zhao Y, Liu Z, Bulterys M, Chen RY. Five-year outcomes of the China National Free Antiretroviral Treatment Program. *Annals of internal medicine* 2009;151(4):241-51, W-52.
7. Chinese Center of Disease and Control. Manual of the National Free Antiretroviral Treatment, 2007 edition 2007.
8. People's Republic of China (2008) UNGASS Country Progress Report. *Beijing: People's Republic of China* 2007.
9. Liu H, Ma Y, Su Y, Smith MK, Liu Y, Jin Y, Gu H, Wu J, Zhu L, Wang N. Emerging trends of HIV drug resistance in Chinese HIV-infected patients receiving first-line highly active antiretroviral therapy: a systematic review and meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014;59(10):1495-502.
10. Djarma O, Nguyen Y, Renois F, Djimassal A, Banisadr F, Andreoletti L. Continuous free access to HAART could be one of the potential factors impacting on loss to follow-up in HAART-eligible patients living in a resource-limited setting: N'djamena, Chad. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2014;108(11):735-8.
11. DeGruttola V, Dix L, D'Aquila R, Holder D, Phillips A, Ait-Khaled M, Baxter J, Clevenbergh P, Hammer S, Harrigan R, Katzenstein D, Lanier R, Miller M, Para M, Yerly S, Zolopa A, Murray J, Patick A, Miller V, Castillo S, Pedneault L, Mellors J. The relation between baseline HIV drug resistance and response to antiretroviral therapy: re-

analysis of retrospective and prospective studies using a standardized data analysis plan. *Antiviral therapy* 2000;5(1):41-8.

12. Liao L, Xing H, Su B, Wang Z, Ruan Y, Wang X, Liu Z, Lu Y, Yang S, Zhao Q, Vermund SH, Chen RY, Shao Y. Impact of HIV drug resistance on virologic and immunologic failure and mortality in a cohort of patients on antiretroviral therapy in China. *Aids* 2013;27(11):1815-24.
13. Hare AQ, Ordonez CE, Johnson BA, Del Rio C, Kearns RA, Wu B, Hampton J, Wu P, Sunpath H, Marconi VC. Gender-specific risk factors for virologic failure in KwaZulu-Natal: automobile ownership and financial insecurity. *AIDS and behavior* 2014;18(11):2219-29.
14. Berg KM, Demas PA, Howard AA, Schoenbaum EE, Gourevitch MN, Arnsten JH. Gender differences in factors associated with adherence to antiretroviral therapy. *Journal of general internal medicine* 2004;19(11):1111-7.
15. Floridia M, Giuliano M, Palmisano L, Vella S. Gender differences in the treatment of HIV infection. *Pharmacological research* 2008;58(3-4):173-82.
16. Moore AL, Mocroft A, Madge S, Devereux H, Wilson D, Phillips AN, Johnson M. Gender differences in virologic response to treatment in an HIV-positive population: a cohort study. *Journal of acquired immune deficiency syndromes* 2001;26(2):159-63.
17. World Health Organization. Surveillance Of HIV Drug Resistance In Adults Receiving Art (Acquired Hiv Drug Resistance). Accessed July 2014. 2014.

18. Bennett DE, Myatt M, Bertagnolio S, Sutherland D, Gilks CF. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. *Antiviral therapy* 2008;13 Suppl 2:25-36.

19. Gaydos CA, Rizzo-Price PA, Balakrishnan P, Mateta P, Leon SR, Verevochkin S, Yin YP, Quinn TC, Strader LC, Pequegnat W, Group NCHSPT. Impact of international laboratory partnerships on the performance of HIV/sexually transmitted infection testing in five resource-constrained countries. *International journal of STD & AIDS* 2011;22(11):645-52.

20. Organization WH. World Health Organization Protocol for Population Based Monitoring of HIV Drug Resistance Emerging During Treatment and Related Program Factors at Sentinel Antiretroviral Therapy Clinics.

21. Jiang Y, Qiu M, Zhang G, Xing W, Xiao Y, Pan P, Yao J, Ou CY, Su X. Quality assurance in the HIV/AIDS laboratory network of China. *International journal of epidemiology* 2010;39 Suppl 2:ii72-8.

22. Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2006;42(11):1608-18.

23. Yan H, Yu H, Xing W, Xiao Y, Zhang H, Pei L, Zhang N, Jiang Y. Development of a proficiency testing program for the HIV-1 BED incidence assay in China. *Scientific reports* 2014;4:4512.

24. Zhong P, Pan Q, Ning Z, Xue Y, Gong J, Zhen X, Zhou L, Sheng F, Zhang W, Gai J, Cheng H, Yue Q, Xing H, Zhuang M, Lu W, Shao Y, Kang L. Genetic diversity and drug

resistance of human immunodeficiency virus type 1 (HIV-1) strains circulating in Shanghai. *AIDS research and human retroviruses* 2007;23(7):847-56.

25. Xing H, Wang X, Liao L, Ma Y, Su B, Fu J, He J, Chen L, Pan X, Dong Y, Liu W, Hsi JH, Yang L, Ruan Y, Shao Y. Incidence and associated factors of HIV drug resistance in Chinese HIV-infected patients receiving antiretroviral treatment. *PloS one* 2013;8(4):e62408.

26. Xing H, Ruan Y, Hsi JH, Kan W, Liao L, Leng X, Wang J, He C, Shao Y. Reductions in virological failure and drug resistance in Chinese antiretroviral-treated patients due to lamivudine-based regimens, 2003–12. *Journal of Antimicrobial Chemotherapy* 2015:dkv078.

27. Nicastri E, Leone S, Angeletti C, Palmisano L, Sarmati L, Chiesi A, Geraci A, Vella S, Narciso P, Corpolongo A, Andreoni M. Sex issues in HIV-1-infected persons during highly active antiretroviral therapy: a systematic review. *The Journal of antimicrobial chemotherapy* 2007;60(4):724-32.

28. Puskas CM, Forrest JI, Parashar S, Salters KA, Cescon AM, Kaida A, Miller CL, Bangsberg DR, Hogg RS. Women and vulnerability to HAART non-adherence: a literature review of treatment adherence by gender from 2000 to 2011. *Current HIV/AIDS reports* 2011;8(4):277-87.

29. Dou Z, Xu J, Jiao JH, Ma Y, Durako S, Yu L, Zhao Y, Zhang F. Gender difference in 2-year mortality and immunological response to ART in an HIV-infected Chinese population, 2006-2008. *PloS one* 2011;6(8):e22707.

30. Sabin LL, Desilva MB, Hamer DH, Keyi X, Yue Y, Wen F, Tao L, Heggenhougen HK, Seton L, Wilson IB, Gill CJ. Barriers to adherence to antiretroviral medications among patients living with HIV in southern China: a qualitative study. *AIDS care* 2008;20(10):1242-50.

31. Feleke Y, Fekade D, Mezegebu Y. Prevalence of highly active antiretroviral therapy associated metabolic abnormalities and lipodystrophy in HIV infected patients. *Ethiopian medical journal* 2012;50(3):221-30.

32. Moyle GJ, Nelson MR, Hawkins D, Gazzard BG. The use and toxicity of didanosine (ddI) in HIV antibody-positive individuals intolerant to zidovudine (AZT). *The Quarterly journal of medicine* 1993;86(3):155-63.

33. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. Geneva, 2013.

34. Dou Z, Zhang F, Zhao Y, Jin C, Zhao D, Gan X, Ma Y. Progress on China' s national free antiretroviral therapy strategy in 2002-2014. *Chinese Journal Epidemiology* 2015;36(12):1345-50.

35. Wester CW, Okezie OA, Thomas AM, Bussmann H, Moyo S, Muzenda T, Makhema J, van Widenfelt E, Musonda R, Novitsky V, Gaolathe T, Ndwapi N, Essex M, Kuritzkes DR, DeGruttola V, Marlink RG. Higher-than-expected rates of lactic acidosis among highly active antiretroviral therapy-treated women in Botswana: preliminary results from a large randomized clinical trial. *Journal of acquired immune deficiency syndromes* 2007;46(3):318-22.

36. Goedecke JH, Micklesfield LK, Levitt NS, Lambert EV, West S, Maartens G, Dave JA. Effect of different antiretroviral drug regimens on body fat distribution of HIV-infected South African women. *AIDS research and human retroviruses* 2013;29(3):557-63.

37. Wu Z, Zhang J, Detels R, Li VC, Cheng H, Duan S, Li Z, Dong L, Huang S, Jia M, Bi X. Characteristics of risk-taking behaviors, HIV and AIDS knowledge, and risk perception among young males in southwest China. *AIDS education and prevention : official publication of the International Society for AIDS Education* 1997;9(2):147-60.

38. Yang H, Li X, Stanton B, Liu H, Liu H, Wang N, Fang X, Lin D, Chen X. Heterosexual transmission of HIV in China: a systematic review of behavioral studies in the past two decades. *Sexually transmitted diseases* 2005;32(5):270-80.

39. Leng X, Liang S, Ma Y, Dong Y, Kan W, Goan D, Hsi JH, Liao L, Wang J, He C. HIV virological failure and drug resistance among injecting drug users receiving first-line ART in China. *BMJ open* 2014;4(10):e005886.

40. Myers Jr SL, Xiaoyan G, Cruz BC. Ethnic minorities, race, and inequality in China: A new perspective on racial dynamics. *Review of Black Political Economy* 2013;40(3):231.

41. Hu J. High Risk Sexual Behavior for HIV/AIDS and Migration Model among Ethnic Minority Migrants in China. *month* 2015;3:0.312.

42. Shou L, WANG QX, Lei N, WU CL, WANG ZF, BAI ZZ, Li L, Peng C, Si Q, LUAN RS. The changing trends of HIV/AIDS in an ethnic minority region of China: modeling the epidemic in Liangshan prefecture, Sichuan Province. *Biomedical and Environmental Sciences* 2013;26(7):562-70.

43. Zhang L, Zhu J, Rui B, Zhang Y, Zhang L, Yin L, Ruan Y, Qian HZ, Shao Y. High HIV risk among Uigur minority ethnic drug users in northwestern China. *Tropical Medicine & International Health* 2008;13(6):814-7.

44. Wang S, Keats D. Developing an innovative cross-cultural strategy to promote HIV/AIDS prevention in different ethnic cultural groups of China. *AIDS care* 2005;17(7):874-91.

45. Huan Z, Fuzhi W, Lu L, Min Z, Xingzhi C, Shiyang J. Comparisons of Adherence to Antiretroviral Therapy in a High- Risk Population in China: A Systematic Review and Meta-Analysis. *PloS one* 2016;11(1):e0146659.

46. Chinese Center for Disease Control and Prevention. Manual of the National Free Antiretroviral Treatment, third edition. Accessed 2013 Jun 12. . 2013.

47. Xing H, Ruan Y, Hsi JH, Kan W, Liao L, Leng X, Wang J, He C, Shao Y, National HWG. Reductions in virological failure and drug resistance in Chinese antiretroviral-treated patients due to lamivudine-based regimens, 2003-12. *The Journal of antimicrobial chemotherapy* 2015;70(7):2097-103.

48. Liao L, Xing H, Shang H, Li J, Zhong P, Kang L, Cheng H, Si X, Jiang S, Li X, Shao Y. The prevalence of transmitted antiretroviral drug resistance in treatment-naive HIV-infected individuals in China. *Journal of acquired immune deficiency syndromes* 2010;53 Suppl 1:S10-4.

49. Zhao K, Kang W, Liu Q, Li Y, Liu Q, Jiang W, Zhuang Y, Guo Z, Yu Z, Li X, Wang C, Yao N, Sun Y. Genotypes and transmitted drug resistance among treatment-naive HIV-1-

infected patients in a northwestern province, China: trends from 2003 to 2013. *PloS one* 2014;9(10):e109821.

50. Su Y, Zhang F, Liu H, Smith MK, Zhu L, Wu J, Wang N. The prevalence of HIV-1 drug resistance among antiretroviral treatment naive individuals in mainland China: a meta-analysis. *PloS one* 2014;9(10):e110652.

51. Jordan MR, Bennett DE, Bertagnolio S, Gilks CF, Sutherland D. World Health Organization surveys to monitor HIV drug resistance prevention and associated factors in sentinel antiretroviral treatment sites. *Antiviral therapy* 2008;13:15.

52. World Health Organization. *Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. World Health Organization; 2013.

Tables/figure

Figure 1. Figure of exclusion on study cohort

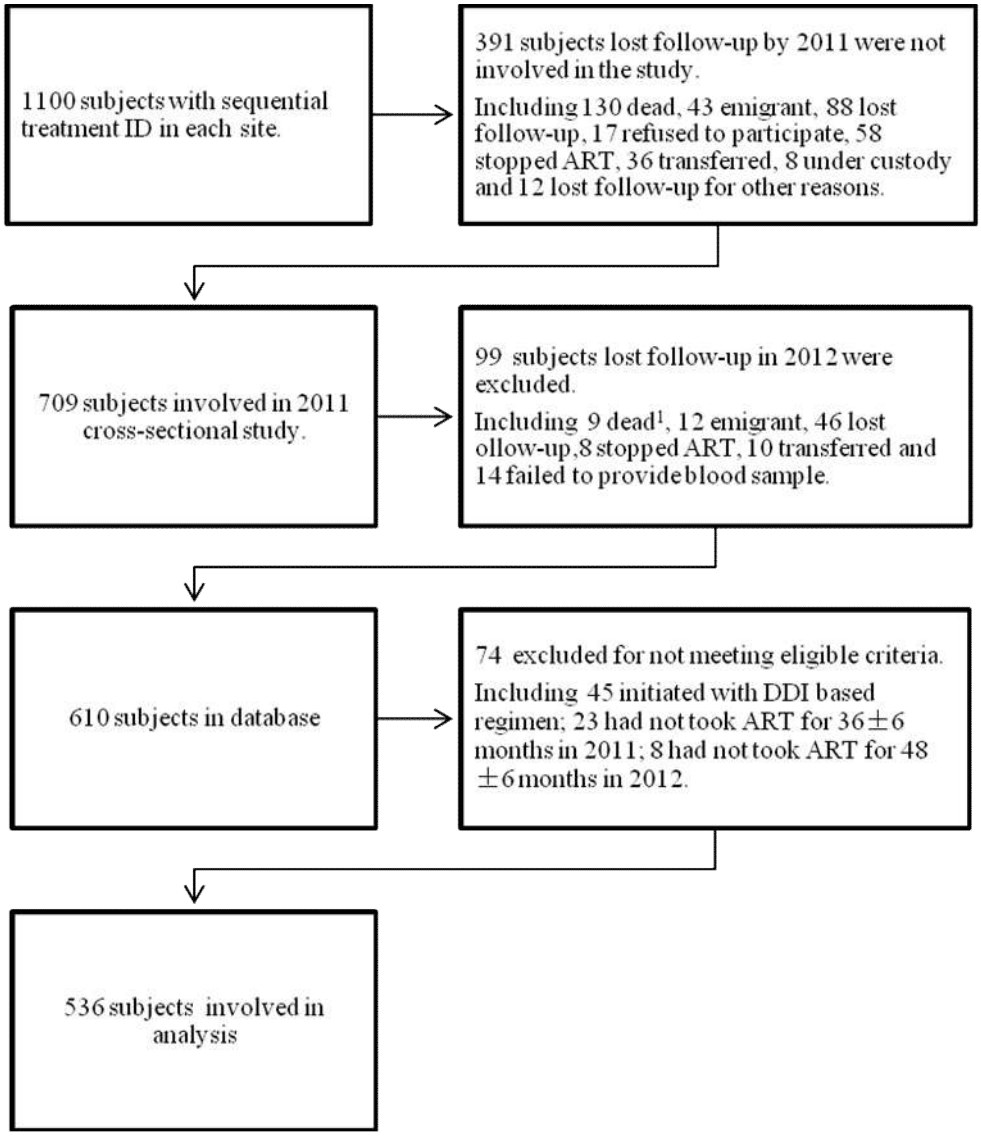

Table 1. Factors associated with virological failure (viral load ≥1000 copies/ml) stratified by sex

Demographic factors								
	Total	Virological failure Risk, N (%)	OR (95%CI)	P-value	Total	Virological failure Risk, N (%)	OR (95%CI)	P-value
Total	258	29 (11.2)			278	34 (12.2)		
Ethnicity								
Han nationality	191	19 (9.9)	1		219	20 (9.1)	1	
Other minorities	67	10 (14.9)	1.6 (0.7,3.6)	0.27	59	14 (23.7)	3.1 (1.5,6.6)	<0.01
Education								
Elementary school or less	134	15 (11.2)	1		107	12 (11.2)	1	
Junior school or more	124	14 (11.3)	1 (0.5,2.2)	0.98	171	22 (12.9)	1.2 (0.6,2.5)	0.68
Marital Status								
Single	59	6 (10.2)	1		75	9 (12)	1	
Married or Cohabited	199	23 (11.6)	1.2 (0.4,3)	0.77	203	25 (12.3)	1 (0.5,2.3)	0.94
Residence								
Rural	197	19 (9.6)	1		172	17 (9.9)	1	
City	61	10 (16.4)	1.8 (0.8,4.2)	0.15	106	17 (16)	1.7 (0.8,3.6)	0.13
Occupation								
Peasant	163	15 (9.2)	1		138	9 (6.5)	1	
Employee	64	11 (17.2)	2 (0.9,4.7)	0.09	114	17 (14.9)	2.5 (1.1,5.9)	0.03
Unemployed	31	3 (9.7)	1.1 (0.3,3.9)	0.93	26	8 (30.8)	6.4 (2.2,18.6)	<0.01
AGE								
<35	73	6 (8.2)	1		53	7 (13.2)	1	
35-45	108	15 (13.9)	1.8 (0.7,4.9)	0.25	119	15 (12.6)	0.9 (0.4,2.5)	0.91
>45	77	8 (10.4)	1.3 (0.4,3.9)	0.65	106	12 (11.3)	0.8 (0.3,2.3)	0.73
Weight(kg)								

<50	89	14 (15.7)	1		49	7 (14.3)	1	
50-70	156	13 (8.3)	0.5 (0.2,1.1)	0.08	193	21 (10.9)	0.7 (0.3,1.8)	0.51
>70	13	2 (15.4)	1 (0.2,4.9)	0.97	36	6 (16.7)	1.2 (0.4,3.9)	0.76
HIV characteristics and treatment factors								
Route of Infection								
Heterosexual Transmission	159	12 (7.5)	1		154	11 (7.1)	1	
Blood Transmission	86	13 (15.1)	2.2 (0.9,5)	0.07	61	10 (16.4)	2.5 (1,6.4)	0.04
Intravenous Drug use	13	4 (30.8)	5.4 (1.5,20.3)	0.01	63	13 (20.6)	3.4 (1.4,8)	0.01
Initial NRTI ART regimen								
AZT based regimen	161	11 (6.8)	1		188	26 (13.8)	1	
D4T based regimen	97	18 (18.6)	3.1 (1.4,6.9)	<0.01	90	8 (8.9)	0.6 (0.3,1.4)	0.24
Switch ART regimen								
No	193	21 (10.9)	1		174	21 (12.1)	1	
Yes	65	8 (12.3)	1.2 (0.5,2.7)	0.75	104	13 (12.5)	1 (0.5,2.2)	0.92
Adverse effects								
No	195	17 (8.7)	1		206	23 (11.2)	1	
Yes	63	12 (19)	2.5 (1.1,5.5)	0.03	72	11 (15.3)	1.4 (0.7,3.1)	0.36
CD4 cell/ml at baseline (2008)								
<350	244	28 (11.5)	1		272	31 (11.4)	1	
≥350	14	1 (7.1)	0.6 (0.1,4.7)	0.62	6	3 (50)	7.8 (1.5,40.2)	0.01
CD4 cell/ml at 36 months (2011)								
0-350	91	18 (19.8)	1		138	21 (15.2)	1	
≥350	167	11 (6.6)	0.3 (0.1,0.6)	<0.01	140	13 (9.3)	0.6 (0.3,1.2)	0.13
CD4 cell/ml at 48 months (2012)								
0-350	81	14 (17.3)	1		122	20 (16.4)	1	

≥350	177	15 (8.5)	0.4 (0.2,1)	0.04	156	14 (9)	0.5 (0.2,1)	0.06
Drug compliance factors								
Missed doses in past month								
No	226	26 (11.5)	1		246	24 (9.8)	1	
Yes	32	3 (9.4)	0.8 (0.2,2.8)	0.72	32	10 (31.3)	4.2 (1.8,9.9)	<0.01
Willing to receive ART in the future								
Always	153	15 (9.8)	1		177	19 (10.7)	1	
Not always	105	14 (13.3)	1.4 (0.7,3.1)	0.38	101	15 (14.9)	1.5 (0.7,3)	0.32
Frequency of taking drugs reminded by friends or relatives								
Often	172	19 (11)	1		168	22 (13.1)	1	
Not often	86	10 (11.6)	1.4 (0.7,3.1)	0.38	110	12 (10.9)	0.8 (0.4,1.7)	0.58
Frequency of taking drugs reminded by doctors								
Often	178	23 (12.9)	1		184	28 (15.2)	1	
Not often	80	6 (7.5)	0.5 (0.2,1.4)	0.19	94	6 (6.4)	0.4 (0.2,1)	0.03

*OR: odds ratio; CI: confidence interval; HIVDR: HIV drug resistance; ART: antiretroviral treatment; AZT: Zidovudine; D4T: Stavudine

Table 2. Factors associated with HIVDR (viral load ≥1000 copies/ml with drug resistance) stratified by sex

Demographic factors								
	Female				Male			
	Total	HIVDR Risk N (%)	OR (95%CI)	P-value	Total	HIVDR Risk N (%)	OR (95%CI)	P-value
Total	258	14 (5.4)			278	13 (2.4)		
Ethnicity								
Han nationality	191	6 (3.1)	1		219	5 (1.2)	1	
Other minorities	67	8 (11.9)	4.2 (1.4,12.5)	0.01	59	8 (6.3)	6.7 (2.1,21.4)	<0.01
Education								
Elementary school or less	134	5 (3.7)	1		107	5 (2.1)	1	
Junior school or more	124	9 (7.3)	2 (0.7,6.2)	0.22	171	8 (2.7)	1 (0.3,3.1)	1
Marital Status								
Single	59	4 (6.8)	1		75	4 (3)	1	
Married or Cohabited	199	10 (5)	0.7 (0.2,2.4)	0.6	203	9 (2.2)	0.8 (0.2,2.8)	0.75
Residence								
Rural	197	7 (3.6)	1		172	5 (1.4)	1	
City	61	7 (11.5)	3.5 (1.2,10.5)	0.02	106	8 (4.8)	2.7 (0.9,8.6)	0.09
Occupation								
Peasant	163	5 (3.1)	1		138	0	1	
Employee	64	6 (9.4)	3.3 (1,11.1)	0.06	114	9 (5.1)	2 (1,12.6)	<0.01
Unemployed	31	3 (9.7)	3.4 (0.8,15)	0.11	26	4 (7)	3 (1,13.4)	<0.01
AGE								
<35	73	5 (6.8)	1		53	6 (4.8)	1	
35-45	108	6 (5.6)	0.8 (0.2,2.7)	0.72	119	6 (2.6)	0.4 (0.1,1.4)	0.15
>45	77	3 (3.9)	0.6 (0.1,2.4)	0.43	106	1 (0.5)	0.1 (0,0.6)	0.02

Weight								
<50	89	8 (9)	1		49	4 (2.9)	1	
50-70	156	4 (2.6)	0.3 (0.1,0.9)	0.04	193	7 (2)	0.4 (0.1,1.5)	0.19
>70	13	2 (15.4)	1.8 (0.3,9.8)	0.47	36	2 (4.1)	0.7 (0.1,3.8)	0.64
HIV characteristics and treatment factors								
Route of Infection								
Heterosexual Transmission	159	8 (5)	1		154	2 (0.6)	1	
Blood Transmission	86	4 (4.7)	0.9 (0.3,3.2)	0.9	61	3 (2)	3.9 (0.6,24.1)	0.14
Intravenous Drug use	13	2 (15.4)	3.4 (0.6,18.2)	0.15	63	8 (10.5)	11.1 (2.3,53.7)	<0.01
Initial NRTI ART regimen								
AZT based regimen	161	5 (3.1)	1		188	10 (2.9)	1	
D4T based regimen	97	9 (9.3)	3.2 (1,9.8)	0.04	90	3 (1.6)	0.6 (0.2,2.3)	0.47
Latest ART regimen								
AZT based regimen	181	8 (4.4)	1		195	12 (3.2)	1	
D4T based regimen	77	6 (7.8)	1.8 (0.6,5.5)	0.28	83	1 (0.6)	0.2 (0,1.5)	0.11
Switch ART regimen								
No	193	10 (5.2)	1		174	6 (1.6)	1	
Yes	65	4 (6.2)	1.2 (0.4,4)	0.76	104	7 (4.1)	2 (0.7,6.2)	0.22
Adverse effect								
No	195	9 (4.6)	1		206	10 (2.5)	1	
Yes	63	5 (7.9)	1.8 (0.6,5.5)	0.32	72	3 (2.2)	0.9 (0.2,3.2)	0.81
CD4 cell at baseline (2008)								
<350	244	14 (5.7)			272	12 (2.3)	1	
≥350	14	0	-	0.36	6	1 (5)	4.3 (0.5,40)	0.2
CD4 cell at 36 months (2011)								
0-350	91	9 (9.9)	1		138	11 (4.8)	1	

≥350	167	5 (3)	0.3 (0.1,0.9)	0.03	140	2 (0.7)	0.2 (0,0.8)	0.02
CD4 cell at 48 months (2012)								
0-350	81	7 (8.6)	1		122	11 (5.4)	1	
≥350	177	7 (4)	0.4 (0.1,1.3)	0.13	156	2 (0.6)	0.1 (0,0.6)	0.01
Drug compliance factors								
Missed doses in past month								
No	226	13 (5.8)	1		246	6 (1.3)	1	
Yes	32	1 (3.1)	0.5 (0.1,4.2)	0.55	32	7 (10.9)	11.2 (3.5,35.9)	<0.01

* ART drug distribution location, Willing to receive ART in the future, Believe ART is health promoting ,Believe poor compliance contribute to HIVDR , Degree of satisfaction on support of friends or relatives, Frequency of taking drugs reminded by friends or relatives, Frequency of taking drugs reminded by doctors are not displayed for no statistical significant difference between categorizes.

* OR: odds ratio; CI: confidence interval; HIVDR: HIV drug resistance; ART: antiretroviral treatment; AZT: Zidovudine; D4T: Stavudine

Table 3. Multivariate Models of Factors associated with virological failure (viral load ≥1000 copies/ml) and HIVDR (viral load ≥1000 copies/ml with drug resistance) stratified by sex

	Female				Male			
	Virological failure		HIVDR		Virological failure		HIVDR	
Variables	Adjusted OR	P-value	Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Total								
Ethnicity								
Han nationality			1		1		1	
Other minorities			4.8 (1.2,19.7)	0.03	2.9 (1.1,7.3)	0.02	12.2 (1.8,84.8)	0.01
Residence								
Rural			1					
City			2.4 (0.6,9.5)	0.22				
AGE								
<35							1	
35-45							0.3 (0.1,1.4)	0.12
>45							0.03 (0,0.6)	0.02
Weight								
<50			1					
50-70			0.3 (0.1,1.1)	0.08				
>70			4.2 (0.6,30.0)	0.15				
Route of Infection								
Heterosexual Transmission	1				1		1	
Blood Transmission	1.2 (0.5,3)	0.74			1.8 (0.6,5.8)	0.33	7 (0.8,64.4)	0.09
Intravenous Drug use	4.1 (1,17.7)	0.06			2.1 (0.8,5.4)	0.12	2.3 (0.3,16.1)	0.41
Initial NRTI ART regimen								
AZT based regimen	1		1					

D4T based regimen	2.5 (1,6.1)	0.04	3.6 (1,12.6)	0.05				
ART drug distribution location								
County hospital or CDC					1			
Township hospital /village clinic /medication monitor					0.5 (0.2,1.3)	0.18		
Adverse effect								
No	1							
Yes	2.3 (1,5.6)	0.06						
CD4 cell at baseline (2008)								
<350					1			
≥350					7.1 (1.1,45.8)	0.04		
CD4 cell at 36 months (2011)								
<350	1		1				1	
≥350	0.4 (0.2,1.1)	0.07	0.3 (0.1,0.9)	0.04			0.3 (0,1.9)	0.2
CD4 cell at 48 months (2012)								
<350	1						1	
≥350	0.6 (0.3,1.6)	0.36					0.1 (0,1)	0.05
Missed doses in past month								
No					1		1	
Yes					2.8 (1.1,7)	0.03	9.7 (2.1,44.1)	<0.01
Frequency of taking drugs reminded by doctors								
Often					1			
Not often					0.4 (0.2,1.2)	0.12		

OR: odds ratio; CI: confidence interval; HIVDR: HIV drug resistance; ART: antiretroviral treatment; AZT: Zidovudine; D4T: Stavudine

Table 4. HIV Drug Resistance and Subtype among 27 patients with HIVDR Mutation Detected at 2011 and/or 2012 stratified by sex

	Female (%)	Male (%)	Mutations	N (%)
Overall	14	13		
Subtype				
B	5 (35.7)	3 (23.1)		
C		1 (7.7)		
CRF01_AE	2 (14.3)	1 (7.7)		
CRF07_BC	7 (50)	8 (61.5)		
Antiretrovial Drug				
Non-nucleoside reverse transcpriptase inhibitors (NNRTI,any)	14 (100)	13 (100)	NNRTI Mutations(total)	27
Efavirenz (EFV)	14 (100)	13 (100)	V90I	1 (3.7)
Nevirapine (NVP)	14 (100)	13 (100)	A98G	2 (7.4)
Etravirine (ETR)	6 (42.9)	8 (61.5)	K101E	6 (22.2)
			K103N	11 (40.7)
			V106A	4 (14.8)
			V108I	6 (22.2)
			E138A	1 (3.7)
			V179D/F	3 (11.1)
			Y181C	5 (18.5)
			G190A	5 (18.5)
			H221Y	1 (3.7)
			P225H	3 (11.1)
			F227L	1 (3.7)
			M230L	1 (3.7)
Nucleoside reverse transcpriptase inhibitors (NRTI,any)	12 (85.7)	9 (69.2)	NRTI Mutations(total）	21
Lamivudine (3TC)	12 (85.7)	9 (69.2)	A62V	1 (4.8)

Azidothymidine (AZT)	2 (14.3)	2 (15.4)	D67G	1 (4.8)
Tenofovir (TDF)	1 (7.1)	3 (23.1)	T69N	2 (9.5)
Stavudine (D4T)	3 (21.4)	3 (23.1)	K70R/Q	4 (19)
Didanosine (DDI)	5 (35.7)	3 (23.1)	V75I/M	2 (9.5)
Abcavir (ABC)	12 (85.7)	9 (69.2)	M184V	17 (81.0)
Emtricitabine (FTC)	12 (85.7)	9 (69.2)	T215N	1 (4.8)
			K219E/Q	2 (9.5)
Protease inhibitors (PI,any)	0	0	PI Mutations(total）	0

*NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors; NRTI: Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; PI: Protease Inhibitor