Prevalence and trends in human immunodeficiency virus-1 subtypes and drug resistance in South Korea: Analysis of 5 years' data (2017-2022)

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Abstract

The clinical guidelines for acquired immunodeficiency syndrome (AIDS) in HIV-infected Koreans recommend routine HIV drug resistance testing for patients undergoing their first highly active antiretroviral therapy or considering a change in medication after 2018. Herein, the trends in HIV-1 subtypes and drug resistance were assessed from 2017 to 2022 by retrospectively analyzing 2,107 HIV-1-infected patients' data. The Stanford HIV Drug Resistance Database was used to analyze each patient's HIV-1 polymerase (*pol*) gene sequences. Subtype B infections were predominant in the study population (75.7%). Meanwhile, CRF01_AE was the most prevalent non-B subtype and increased from 58.4% to 73.7% during the study period. Overall, all types of drug resistance mutations (DRM) were detected in 34.7% of the HIV-1 pol sequences. The prevalence of DRMs and high-level resistance mutations decreased from 39.4% to 31.6% and 16.7% to 7.7%, respectively. The prevalence of DRM was higher in patients treated with antiretroviral therapy (ART). These findings indicate that the prevalence of non-B subtype HIV infection has increased rapidly in South Korea, and the overall prevalence of DRMs decreased between 2017 and 2022. Additionally, since DRM is high in ART-treated patients, routine standard genotypic resistance testing surveillance is important before and after the treatment.

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Running title: HIV-1 subtypes and resistance in South Korea

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ABSTRACT

The clinical guidelines for acquired immunodeficiency syndrome (AIDS) in HIV-infected Koreans recommend routine HIV drug resistance testing for patients undergoing their first highly active antiretroviral therapy or considering a change in medication after 2018. Herein, the trends in HIV-1 subtypes and drug resistance were assessed from 2017 to 2022 by retrospectively analyzing 2,107 HIV-1-infected patients' data. The Stanford HIV Drug Resistance Database was used to analyze each patient's HIV-1 polymerase (*pol*) gene sequences. Subtype B infections were predominant in the study population (75.7%). Meanwhile, CRF01_AE was the most prevalent non-B subtype and increased from 58.4% to 73.7% during the study period. Overall, all types of drug resistance mutations (DRM) were detected in 34.7% of the HIV-1 pol sequences. The prevalence of DRMs and high-level resistance mutations decreased from 39.4% to 31.6% and 16.7% to 7.7%, respectively. The prevalence of DRM was higher in patients treated with antiretroviral therapy (ART). These findings indicate that the prevalence of non-B subtype HIV infection has increased rapidly in South Korea, and the overall prevalence of DRMs decreased between 2017 and 2022. Additionally, since DRM is high in ART-treated patients, routine standard genotypic resistance testing surveillance is important before and after the treatment.

Key words: HIV-1 subtypes, drug resistance mutation, highly active antiretroviral therapy, genotypic antiretroviral resistance test, standard genotypic resistance testing

INTRODUCTION

Global efforts to prevent the spread of human immunodeficiency virus (HIV) have reduced the incidence of new infections [1]. The importance of wide coverage and effective suppression of HIV viremia is reflected by the 90-90-90 goals established by the Joint United Nations Program on HIV/AIDS. In addition, Korea's national health insurance fully covers HIV-related medical expenses for those subscribed to the program to ensure that no patient is untreated for economic reasons.

Highly active antiretroviral therapy (HAART) has significantly reduced HIV-related morbidity and mortality [2]. Recent guidelines emphasize that antiretroviral therapy (ART) should be initiated immediately after diagnosis to reduce the risk of HIV transmission and improve the rate of virologic suppression[3,4]. However, the increase in ART use is expected to increase the prevalence of acquired drug resistance among patients infected with HIV undergoing treatment and transmitted drug resistance (TDR) in newly infected patients [5]. Moreover, these drug-resistant mutations (DRM) can be transferred to treatment-naïve patients, thereby negatively affecting the success of primary care and individual prognosis [6].

Current treatment guidelines for using antiretroviral agents against HIV-1 suggest that therapy for a treatment-naïve patient comprises two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active drug from one of three drug classes: integrase strand transfer inhibitor (INSTI), nonnucleoside reverse transcriptase inhibitor (NNRTI), or protease inhibitor (PI) [3,4]. The introduction of INSTIs is expected to change TDR demographics in treatment-naïve patients. Furthermore, the emergence of INSTI resistance mutations has been reported [7], including a major INSTI resistance mutation, E92Q, in treatment-naive patients in South Korea[8]. These results suggest the need for routine monitoring of TDR, including INSTI resistance mutations.

Since 2011, new antiretroviral drugs, such as etravirine (NNRTI) and darunavir (PI), have been frequently prescribed in South Korea. HIV drug resistance testing has been performed to assist in selecting active drugs when altering ART regimens, especially in patients with virologic failure. The clinical guidelines for HIV/AIDS in HIV-infected Koreans[9] after 2018 recommend routine HIV drug resistance testing of patients undergoing their first HAART or those considering a change in medication due to virologic failure. The prevalence of HIV TDR in South Korea was 2.5–12.0% between 1999 and 2019, showing an increasing tendency over time [10-13].

In South Korea, the most common subtype of HIV-1 is subtype B. In fact, a nationwide study involving sample collection between 1999 and 2012 revealed that 93.1% of the samples were subtype B [14]. In South

Korea, subtype B primarily comprises Korean clade B (B^k), a distinct clade from subtype B in other countries, likely due to isolation from other geographic locations[15]. However, a recent study reported an increase in non-B subtypes from 13.4% to 27.4% between 2015 and 2019, with CRF01_AE being the most prevalent non-B subtype [16].

As of December 2021, the cumulative number of patients with HIV infection in Korea, including non-ethnic Koreans, was 20,715. Approximately 1,000 new HIV cases have been reported annually since 2013, with 90% of the patients being Korean and 10% non-ethnic Koreans[17]. The centralized laboratory conducted more than 600 genotypic antiretroviral resistance test (GART) annually from hospitals across the country since 2017; hence, more than half of patients with HIV in Korea have undergone HIV-drug resistance (DR) testing at the study institution. Therefore, the analysis conducted by this institution might represent the current HIV-1 drug resistance status and subtype statistics throughout South Korea. Accordingly, this study assesses the trends in HIV-DR and HIV-1 subtypes based on this large sample population.

MATERIALS AND METHODS

Study design and patient population

Genotypic antiretroviral resistance test (GART) data for 2,107 patients infected with HIV-1 between August 2017 and August 2022 at Severance Hospital, Seoul, South Korea, were retrospectively analyzed. The clinical data included the patients' medical records. Treatment information, including antiviral agents used, was only collected from the patients' medical records at Severance Hospital. The study protocol was reviewed and approved by the institutional review board of Severance Hospital in Seoul, Korea (IRB No. 4-2019-1076). The requirement for written informed consent was waived due to the study's nature (review of medical records)—the study involved no more than minimal risk to the patients, and their privacy was thoroughly protected.

Sequencing of HIV-1 polymerase (*pol*) (protease and reverse transcriptase genes)

HIV RNA was extracted from plasma using the QIAmp Viral RNA Mini Kit (QIAGEN, Hilden, Germany) and reverse-transcribed into complementary DNA (cDNA) using the RETROscript kit (Applied Biosystems, Foster City, CA, USA), according to the manufacturer's instructions. A nested polymerase chain reaction (PCR) was performed using 10 µL of diluted cDNA or cellular DNA template added to 40 µL of the reaction mixture for the first round. The reaction mixture comprised 5.0 µL of 10× PCR buffer containing magnesium chloride and 1.0 µL of 10 nM deoxynucleotide triphosphate Mix (GeneAmp, Applied Biosystems, Foster City, CA, USA), 0.25 µL of Taq DNA Polymerase (Roche Diagnostics, Indianapolis, IN, USA), 31.75 µL of molecular grade water, and 1 µL of each of the 20 µM primers. The 50-µL samples were heated to 94 °C for 2 min and subjected to 35 cycles of 30 s at 94 °C, followed by 30 s at 52 °C and 60 s at 68 °C. Subsequently, the samples were heated to 68 °C for 10 min and stored at 4 °C until use. The second round of PCR was performed using 5 µL of the product from the first round as the template, which was added to 45 µL of the reaction mixture to obtain a final volume of 50 µL. This reaction mixture comprised the same reagents, with the volume of molecular-grade water increased to 36.75 µL. The thermal cycling parameters were: 35 cycles of 30 s at 94 °C, followed by 30 s at 55 °C and 60 s at 72 °C. The PCR products from each sample were sequenced using Prism Dye terminator kits (ABI) on an ABI 3730 DNA Analyzer (Applied Biosystems, Foster city, CA, USA).

HIV-1 drug resistance and subtype analysis

Antiretroviral resistance mutations and subtype analysis were identified using the HIVdb program of the Stanford University HIV Drug Resistance Database (*http://hivdb.stanford.edu*; version 9.1, Algorithm Date: 2 June 2022) [18]. The sum of the average resistance mutation scores in each patient's HIV-1 polymerase (*pol*) gene sequences, comprising protease, reverse transcriptase, and integrase, was obtained from the Stanford HIV Drug Resistance Database (HIVdb). The drug resistance intensity was classified as S (susceptible, potential low-level resistance), I (low or intermediate level resistance), or R (high-level resistance), based on the Stanford HIVdb algorithm results.

Statistical analysis

Chi-squared test or Fisher's exact test was used to compare categorical variables, and the Kruskal–Walli's test was used for comparisons between subtypes. Statistical analysis was performed using the R Statistical software (v.4.2.1), where P values < 0.05 were considered significant.

RESULTS

This study included data collected from 274 patients from Severance Hospital and 1,833 patients from 55 other hospitals across South Korea (Figure 1). The 55 hospitals included 19 in Seoul, 12 in Gyeonggi-province, 4 in Incheon, 2 in Daejeon, 2 in Daegu, 2 in Busan, 2 in Gwangju, 3 in Gangwon-province, 2 in Gyeongsangbuk-province, and 3 each in Chungcheongnam-province, Gyeongsangnam-province, Jeollabuk-province, and Jeollanam-province. A total of 2,360 samples were collected, including 253 follow-up samples.

Study population and demographic features

The demographic and clinical characteristics of the 2,107 patients are summarized in Supplementary Table 1. Most patients included in the study were Koreans (92.2%, 1943/2107) and men (93.3%, 1966/2107), with a median age of 37.2 (20.1-85.5) years. In a subgroup of the Severance Hospital patients, 81% were ART-naive and 19% were ART-treated. Subtype B infections were predominant in the total study population at 75.7% (1595/2107). Non-B subtype strains were identified in 24.3% (512/2107) of the patients.

Several demographic features differed in the sub-group analysis. Women were more likely to harbor non-B infections (51.8%, 73/141) than men (22.3%, 439/1966). The difference in the mean age between women and men was significant (44.5 vs. 40.4 years, P [?] 0.001). Women's ethnicity was more likely to be non-Korean (26.2%, 37/141) compared with men's ethnicity (6.5%, 127/1966; Supplementary Table 2). Koreans were more likely to harbor Subtype B infections (79.9%, 1553/1943) than non-Korean (25.6%, 42/164). The difference in the mean age between Koreans and non-Koreans was significant (40.9 vs. 38.0 years, $P = 0.001$). The rate of harboring high-level-resistance between Koreans and non-Koreans did not differ significantly (12.5% vs. 9.8%, $P = 0.365$; Supplementary Table 3). Moreover, there was no statistically significant difference in the HIV-1 subtype distribution between patients from Severance Hospital and those from other hospitals in South Korea ($P = 0.544$; Supplementary Table 4).

Subtype trends of HIV-1

Temporal trends showed that the proportion of non-B subtype infection increased during the observation period from 15.3% before 2018 to 33.3% in 2022, stratified by the initial diagnosis of HIV infection (Figure 2). Among the 512 patients with non-B subtype infections, CRF01_AE (64.8%, 332/512) was the most prevalent, followed by CRF02_AG (10.9%, 56/512), subtype A (10.4%, 53/512), CRF56_cpx (4.7%, 24/512), subtype C (3.7%, 19/512), CRF07_BC (2.3%, 12/512), subtype G (1.0%, 5/512), and other subtypes (2.1%, 11/512) such as CRF06_cpx, CRF55_01B, and subtype D. The distribution within non-B subtypes also changed over time. The proportion of CRF01_AE increased from 58.4% to 73.7% from 2018 to 2022, whereas that of CRF02_AG decreased from 11.7% to 3.0%.

Correlation between DRMs and virus subtypes

There were 547 (34.3%) subtype B, 117 (35.2%) CRF01_AE, 19 (33.9%) CRF02_AG, 26 (49.1%) subtype A, 2 (8.3%) CRF56_cpx, 7 (36.8%) subtype C, 4 (33.3%) CRF07_BC, and 9 (56.3%) other subtypes in the study cohort. Overall, 731 (34.7%) HIV-1 *pol* sequences with one or more DRMs were detected. High-level DRM was detected in 12.3% (259/2107) of patients. The DRM profile differed in CRF01_AE, CRF02_AG, and subtype A. The proportion of six mutations, A62V (NRTI), K219E/Q/N/R (NRTI), E138A/G/K (NNRTI), V179F/D/E (NNRTI), Y181C/V/I/F (NNRTI), and Y188C/L/H (NNRTI), differed significantly among subtypes ($P < 0.05$; Table 1). The percentage of the NRTI mutation A62V was high in subtype A (32.1%) and low in subtype B (0.7%). NRTI mutations K219E/Q/N/R were observed frequently in CRF01_AE (2.4%) and CRF02_AG (5.4%), compared with that in the study cohort (1.1%). Moreover, NNRTI mutations, E138A/G/K (10.7%) and Y181C/V/I/F (7.1%), were observed frequently in CRF02_AG. In contrast, the

PI mutation, M46I/L, was observed only in subtype B (0.9%) and CRF01_AE (0.6%). The most frequent DRM in all subtypes was V179F/D/E (11.1%).

Trends in DRM prevalence

The initial samples for 2,107 patients collected over 5 years were assessed. The overall prevalence of DRMs, including all DRM types (low-level, intermediate, and high-level mutations), declined from 39.4% before 2018 to 31.6% in 2022 (Figure 3). The prevalence of high-level resistance mutations, which are more clinically significant, also declined from 16.7% to 7.7% between 2018 and 2022. The DRM trends in NRTIs and INSTIs decreased from 14.5% to 6.4% and 8.0% to 1.7%, respectively, whereas NNRTIs showed a lateral trend from 27.7% to 26.3%. The DRM trends in PIs declined steadily from 39.4% to 31.6%.

Acquired drug-resistant mutation prevalence in ART-treated patients

The DRM prevalence was compared between ART-naive ($N = 222$) and ART-treated groups ($N = 53$) at Severance Hospital (Figure 4) to evaluate the percentage of transmitted drug resistance mutations (TDRM) and acquired drug resistance mutations to four classes of antiretroviral drugs. The NNRTIs resistance was common in ART-naive (26.1%) and ART-treated (42.3%) patients. The prevalence of DRM was higher in ART-treated patients: NRTIs (36.5% vs. 6.3%), PIs (9.6% vs. 0.9%), and INSTIs (26.9% vs. 2.7%). These differences were high in dual-class resistance: NRTI + NNRTI (19.2% vs. 3.6%), NRTI + PI (5.8% vs. 0.5%), NNRTI + PI (9.6% vs. 0.5%), NRTI + INSTI (21.2% vs. 1.4%), and NNRTI + INSTI (15.4% vs. 1.4%).

Additionally, 428 samples collected from 172 patients revealed that the median observation time was 9 months (2–47 months). Comparing the baseline samples of patients to the follow-up samples, all DRM types (low-level, intermediate, and high-level mutations) increased from 44.2% to 51.6%. The high-level mutations increased from 24.4% to 28.9% (Supplementary Table 5).

DISCUSSION

In the current study, the prevalence of HIV-1 subtypes and drug resistance in South Korea was assessed between 2017 and 2022. The prevalence of TDR in South Korea reportedly ranges from 2.5% to 12.0%; however, it varies considerably in different studies[10-13]. For instance, Jung et al. showed that TDR increased between 2011 and 2019 (5.1%-7.2%)[12], while Park et al. reported no significant increase in TDR between 1999 and 2012 [11]. These discrepancies might be due to the analysis of a small fraction of patients with HIV-1 in South Korea, with a maximum of 141 patients being diagnosed yearly (range: 27-141). To date, the current study is the largest-scale study, comprising 2,107 patients, to estimate TDRM in South Korea. More than half of the patients with HIV-1 diagnosed nationwide between 2017 and 2022 were included in this analysis. Moreover, while previous DRM studies only reported the resistance trends of NRTIs, NNRTIs, and PIs[11,12], the present study analyzed INSTI mutations and is the first to report the trends in INSTI resistance mutations in South Korea.

In a previous analysis of the HIV-1 subtypes reported between 2005 and 2009, approximately 90% were subtype B; CRF02_AG was the most common among the non-B subtypes, followed by CRF01_AE and subtype A1[14,19]. Meanwhile, a recent study analyzed HIV-1 subtypes between 1999 and 2018 and showed that subtype B infections were more predominant (78.7%) than non-B subtypes (21.3%), which increased to 27.4% between 2015 and 2019 in Busan, Korea [16]. Lee et al. also reported CRF01_AE (52.7%) as the most common non-B subtype, followed by CRF02_AG, subtype A1 [16]. Similarly, in the present analysis between 2017 and 2022, subtype B infections were predominant (75.7%). Non-B subtype strains were identified in 24.3% of patients. CRF01_AE (64.8%) was the most prevalent in non-B subtype infections, followed by CRF02_AG (10.9%) and A1 (10.4%). Although the overall prevalence of subtype B was similar to that reported by previous studies [14,16,19], when stratified by year, the current analysis showed a rapid increase in non-B subtypes from 20% to 33.3% between 2019 and 2022, thus increasing by 4.4% each year. This increase in non-B subtypes is driven primarily by the rapid expansion of the CRF01_AE population, which increased from 58.4% to 73.7% in the non-B subgroup between 2017 and 2022. However, CRF02_AG decreased from

11.7% to 3.0%, whereas subtype A1 remained relatively consistent during the same period. These results are related to the rapid increase in the number of Chinese immigrants, primarily carrying CRF01_AE (around 50%) [20,21], from 0.1 million to 1.1 million between 2000 and 2019, accounting for approximately 50% of all immigrants [22]. Moreover, subgroup analysis showed that patients of Korean ethnicity largely carried subtype B compared with non-Korean patients (79.9% vs. 25.6%). Women were also more likely to harbor non-B subtypes than men (51.5% vs. 22.3%). These results are consistent with those of a previous study[16].

The current study DRM data showed that 34.7% of the HIV-1 sequences harbored DRMs (low-, intermediate-, or high-level). However, only high-level DRMs, which are clinically significant, were detected in 12.3% of patients. These results showed a higher prevalence of DRMs than previous reports in South Korea (range: 2.5% to 12.0%)[10-13]. The criteria for defining DRMs can lead to differences in estimation of the prevalence of DRM by studies that include only high-level resistance or all types of DRM. Indeed, the prevalence of high-level DRMs in the current study is higher than that of a previous global study [23], which conducted a meta-analysis of 149 studies, including five from upper-income Asian countries (12.3% vs. 8.7%). However, the prevalence results of this study may be exaggerated as INSTI mutations were also included, unlike previous studies.

Certain mutations exhibited significantly different percentages in different sub-types. For instance, the NRTI mutation A62V was observed in 32.1% and 31.4% of patients harboring subtype A and A6, respectively [24]; meanwhile, the PI mutation M46I/L was observed only in 0.9% and 0.6% of patients harboring subtype B and CRF01_AE, respectively. These results are consistent with a previous Chinese HIV-1 subgroup analysis [21]. Moreover, the prevalence of DRM declined over the 5 years of the study period. All mutation types declined from 39.4% to 31.6%. High-level resistance mutations also decreased from 16.7% to 7.7%, and the prevalence of NRTI and INSTI DRMs decreased. However, no significant change was observed in NNRTI or PI. These declining trends in drug resistance are not common globally. In fact, most previous reports have demonstrated an overall increase in drug resistance [1,21,23] with only a few noting decreases in TDRM prevalence. That is, Tostevin et al. observed a decrease in DRMs between 2010 and 2013. However, it was confined to the men who have sex with men population, and the rates remained stable in those with heterosexually acquired HIV infections[25]. Weng et al. observed a stable resistance prevalence between 2009 and 2015 (slope = -0.086) under a fixed regimen with zidovudine/lamivudine + efavirenz or nevirapine as the first-line therapy [26]. These TDRM trends are affected by environmental and economic factors, including the COVID-19 pandemic. In fact, a recent study conducted in Canada revealed that drop-in services and outreach work by commercial sex workers were reduced due to COVID-related restrictions [27]. Access to healthcare also declined significantly during the COVID-19 pandemic.[28]. These unusual decreases in TDRM were observed in countries with national health insurance (NHI) systems, which fully cover HIV-related medical expenses for NHI subscribers to ensure the treatment of all patients. These results show that accessibility to ART can play an essential role in changing TDRM trends. Additionally, the adoption of pre-exposure prophylaxis treatment since 2018 in South Korea may have affected the TDRM trends.

Additionally, NNRTI resistance was detected in 26.1% and 42.3% of patients in the ART-naive and ART-treated groups, respectively. The prevalence of DRM was higher for NRTIs (36.5% vs. 6.3%), PIs (9.6% vs. 0.9%), and INSTIs (26.9% vs. 2.7%) in ART-treated patients. These differences were more significant in dual-class resistance: NRTI + NNRTI (19.2% vs. 3.6%), NRTI + PI (5.8% vs. 0.5%), NNRTI + PI (9.6% vs. 0.5%), NRTI + INSTI (21.2% vs. 1.4%), and NNRTI + INSTI (15.4% vs. 1.4%). Similar results have been demonstrated in previous studies[21,29]. These findings underscore the need to implement surveillance programs for HIV drug resistance in clinical management.

The current study has certain limitations. First, this was a nationwide multi-hospital-based, retrospective, observational study. The collection of clinical and epidemiological information was limited due to insufficient information provided to the centralized laboratory from hospitals that requested sample analysis. Second, the analysis comparing ART-naive and ART-treated groups was performed on a limited number of patients. However, this was accounted for by performing a subtype distribution analysis and confirming that patients enrolled at Severance Hospital were representative of the whole cohort to some extent (Supplementary Table

4). Third, despite efforts to clearly classify medical records, clinical information for some patients in the ART-treated group before 2018 may be inaccurate. GART was adopted as a routine surveillance test for HIV-1 treatment in 2018 in South Korea[9]. Therefore, the GART results before 2018 were primarily weighted toward ART-treated patients, especially those who were ART-resistant. This could have exaggerated the prevalence of DRM before 2018. Fourth, it is difficult to directly compare DRM prevalence between studies as the algorithm version used in each study differs. That is, each study used a different mutation analysis program or version, even if the Stanford University HIV Drug Resistance Database was applied. In particular, the Stanford University HIV Drug Resistance Database accumulates more mutation data with each version update. Therefore, if researchers analyze a previous sequence with a newer version, the results could be different.

CONCLUSIONS

To date, this is the largest South Korean study on HIV-1 subtype analysis and drug resistance surveillance, presenting the overall prevalence of TDRM from 2017 to 2022. The proportion of non-B subtypes of HIV-1 infections has recently increased rapidly, with CRF01_AE becoming the predominant non-B subtype in South Korea. Moreover, an overall decrease in TDRM was observed in recent years. In particular, TDRM prevalence decreased in NRTIs and INSTIs. However, considering that DRMs are detected in more than 20% of ART-naive patients, routine GART is strongly recommended before ART treatment. Routine GART surveillance will also improve HIV prevention and control the development of drug resistance.

Declaration of competing interest

All authors declare no competing interests.

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Ethical Approval statement

This study protocol was reviewed and approved by the institutional review board of Severance Hospital in Seoul, Korea (IRB No. 4-2019-1076).

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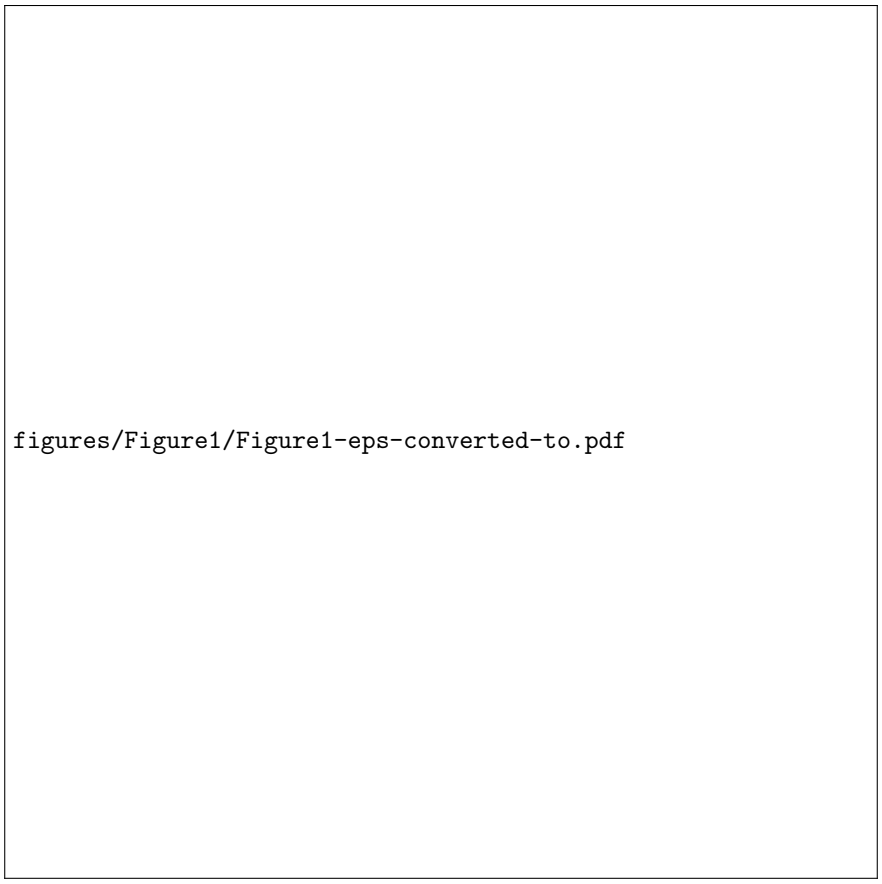
FIGURE LEGENDS

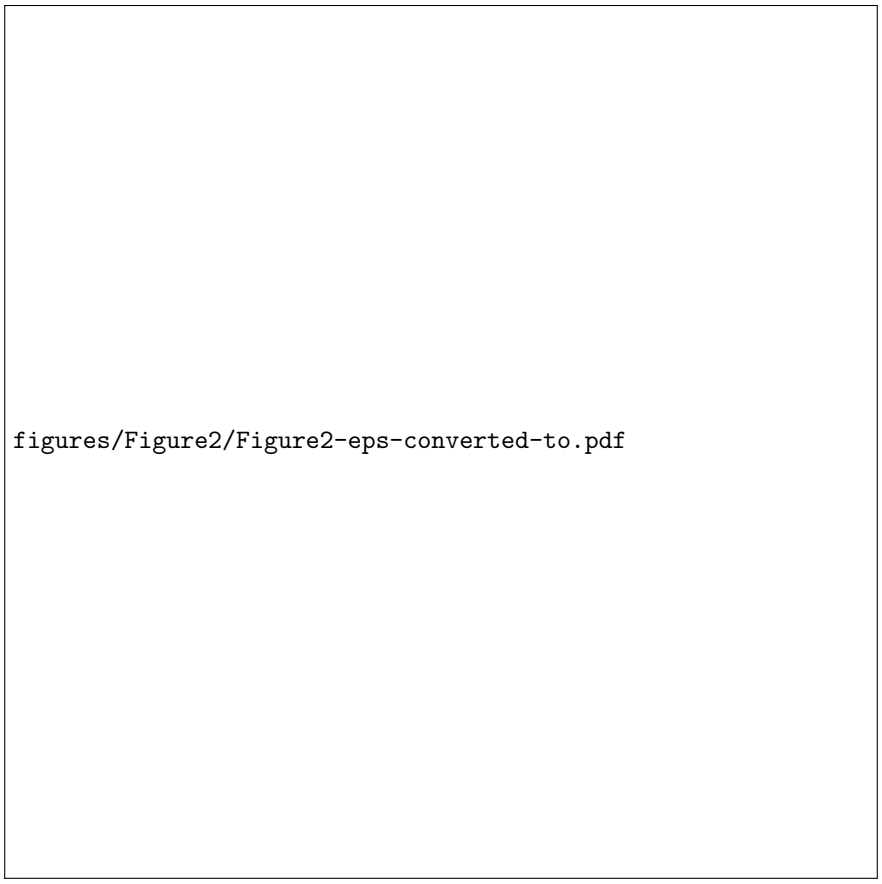
Figure 1. Flow diagram of patient enrollment

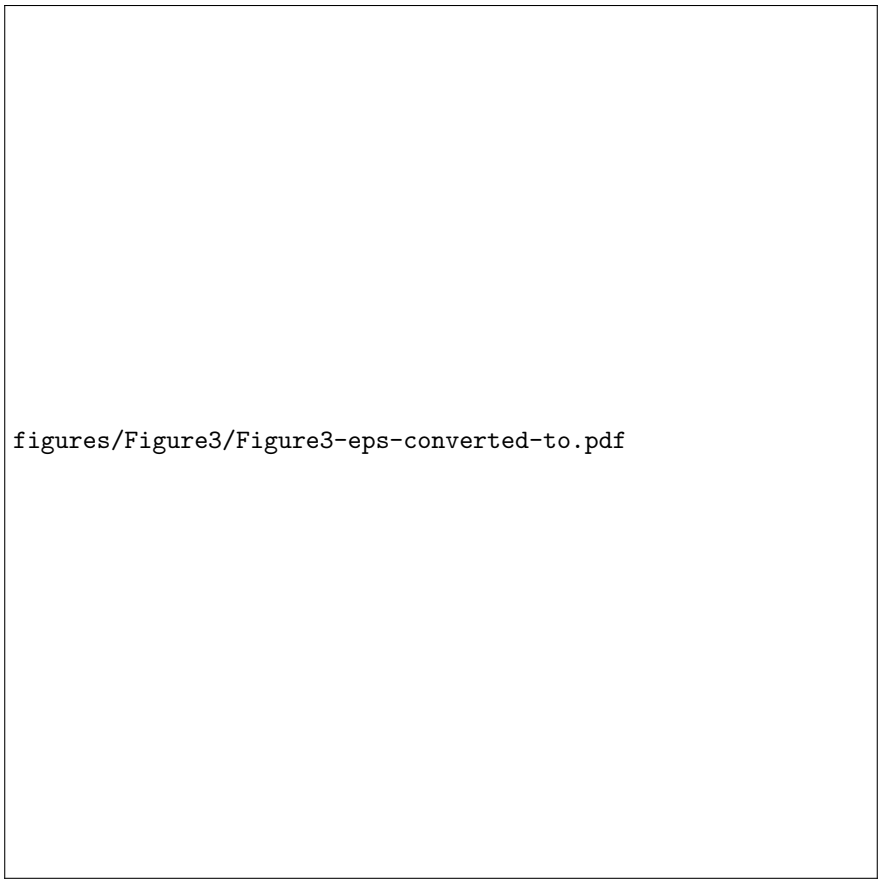
Figure 2. Trends in the proportion of HIV-1 B/non-B subtypes and changes in the distribution of non-B HIV-1 subtypes, stratified by HIV diagnosis year.

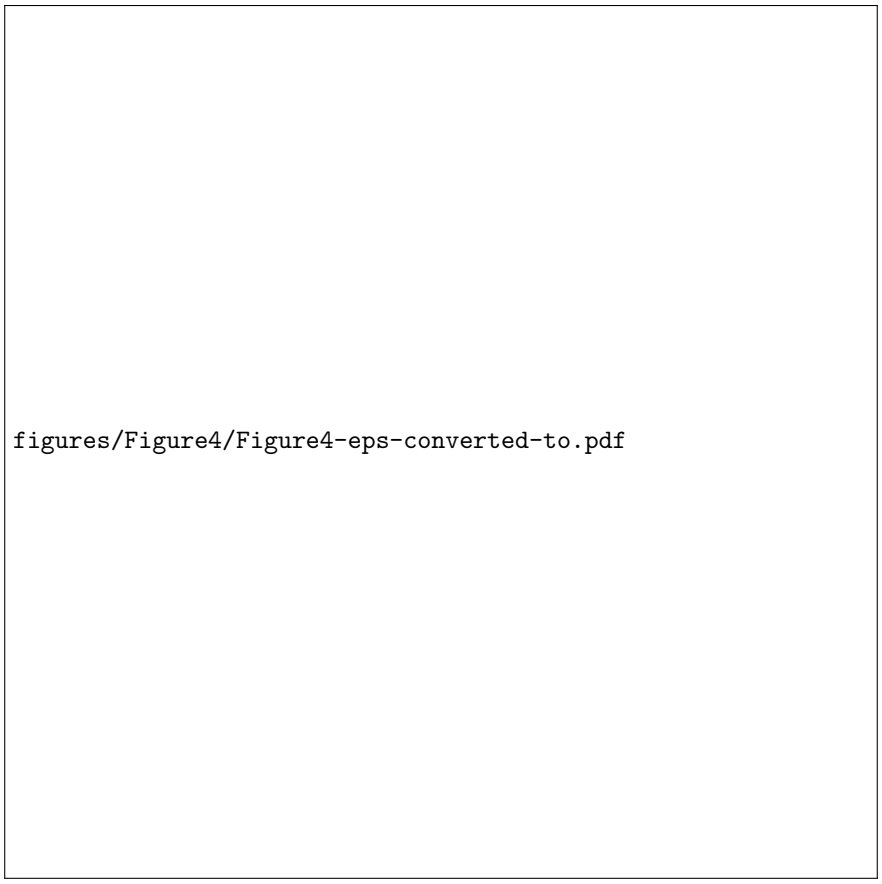
Figure 3. Drug resistance mutation trends over 5 years

Figure 4. Prevalence of DRM between ART-naive and ART-treated patients at Severance Hospital









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