Antiretroviral Therapy Switch Rates and Switching Patterns In 16,069 People Living with HIV: A Nationwide, Population-Based Study in Japan

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Research Article

Keywords: Antiretroviral therapy, Switch rate, Time-to-switch, Integrase strand transfer inhibitor, National Database of Health Insurance Claims and Specific Health Checkups of Japan, Claims database study, Asia, Japan

Posted Date: July 10th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-691735/v1

Abstract

To report the status of switch rates and time-to-switch of antiretroviral therapy (ART) regimens by evaluating anchor drug classes and common switching patterns in Japanese people living with human immunodeficiency virus (HIV, PLWH). This cross-sectional cohort study extracted data of 28,089 PLWH from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), which contains data representing the entire population of Japan. PLWH with first prescription records of ART administered between January 2011 and March 2019 were identified (n = 16,069). The median time-to-switch and switch rates of anchor drug classes were estimated by Kaplan-Meier analysis. Brookmeyer-Crowley and Greenwood methods were used to estimate 95% confidence intervals for switch rates and median days, respectively. Switch rates were compared between anchor drug classes by year using log-rank tests. A total of 3,108 (19·3%) PLWH switched anchor drug classes from first to second regimens. Switch rates increased continuously over eight years for non-nucleoside reverse transcriptase inhibitors (NNRTIs) (14·9%–65·5%) and protease inhibitors (PIs) (13·2%–67·7%), with median time-to-switch of 1,826 and 1,583 days, respectively. Integrase strand transfer inhibitors (INSTIs) maintained a low switch rate (3·0%–7·6%), precluding median-days calculation. The majority of patients treated initially with NNRTIs and PIs switched to INSTIs regardless of switching times (< 1 year: 67·3% and 85·9%, respectively; ≥1 year: 95·5% and 93·6%, respectively). The foremost switching strategies for first-to-second ART regimens are from NNRTI or PI to INSTI regimens that maintain low switch rates long term. INSTI HIV agents may be the most durable anchor drug class for PLWH receiving ART.

Introduction

Antiretroviral drugs are being used globally to treat people living with human immunodeficiency virus (HIV, PLWH). International and national guidelines stipulate that durable, straightforward antiretroviral therapy (ART) regimens are the main focus of lifelong chronic HIV treatment.[1–3] Administration of ART regimens supports immune system function, reduces complications, and improves quality of life,[4] decreasing morbidity and mortality. Increased survival rates among PLWH are attributed to successful ART.[5–7] Life expectancy for PLWH now approximates that of HIV-negative individuals.[8,9]

Nevertheless, PLWH frequently switch ART regimens during chronic HIV treatment. Changes may occur because patients or clinicians think a new medication may produce better results or patients' may become dissatisfied with their current regimen. Drug toxicity, unsatisfactory levels of viral suppression, drug-related adverse events (AEs), or just simplification of a regimen may also prompt a switch.[10–12] However, no consensus exists regarding switching strategies, and though changes occur frequently, switching strategies remain to be clearly defined.

The absence of a standard switching strategy makes it imperative to fully understand the circumstances most often leading to ART regimen switches and the anchor drug classes involved. Anchor drug classes that tend to be administered for longer durations also need to be identified.

Five classes of antiretroviral medications are used in Japan: nucleoside reverse transcriptase inhibitors (NRTIs), nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and entry inhibitors (EIs).[3] The most recent guidelines for initiating an ART regimen recommend combination regimens (cART) consisting of two NRTIs as backbone therapy, with a third “anchor” drug from another class, most often NNRTIs, PIs, or INSTIs.[1–3] Clinicians’ selection of an anchor drug is central to the treatment strategy because backbone choices are comparatively limited.

Our previous study was a preliminary assessment of switch rates and time-to-switch of ART regimens using a hospital claims database with a distinctly smaller dataset of eligible HIV-positive patients than that in the larger nationwide dataset used for the present study.[13] We hypothesized that expanding the data source would not only confirm our preliminary results, but also update our knowledge of current switching rates and patterns observed nationwide. Therefore, we used the nationwide database, the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), which contains data representing the entire population in Japan, to confirm and update our preliminary findings and identify the most effective ART approaches for long-term treatment of PLWH in Japan.

Methods

Study design and data source

This observational, retrospective cohort study extracted patient data from the Japanese National Database (NDB) for HIV-positive patients who received treatment between April 2009 and March 2019.[14] The NDB is the largest nationwide cross-sectional database in Japan, and it contains comprehensive health insurance claims records from the National Health Insurance system of Japan for direct primary care delivered as inpatient care. The NDB has been used to supported clinical studies.[15,16] The NDB includes data for diagnoses, age, sex, dates of outpatient services, dates of admission and discharge, procedures undertaken, prescribed drugs, etc. Patients treated from April 2009 to March 2019 with at least one diagnosis and any treatment processed in the claims data were enrolled. All included diagnoses were categorized according to the “The International Classification of Disease, 10th Revision, Clinical Modification” (ICD-10) diagnostic system. Patients with a diagnostic code of HIV-2 infection were excluded.

All insurance claims data are deidentified by the Ministry of Health, Labour and Welfare, and the ministry’s guidelines on information security were followed in the study. To ensure patient privacy, inspection by and permission from the Ministry for publication is required before submission of the draft manuscript.

Study population

HIV-positive patients in the database were identified by the presence of at least one record of the International Classification of Diseases 10th Revision (ICD-10) codes B20—24, including: HIV disease

resulting in infectious and parasitic diseases (B20), malignant neoplasms (B21), other specified diseases (B22), other conditions (B23), and unspecified HIV disease (B24). To avoid including doubtful HIV-positive patients (i.e., poorly recorded or intentionally recorded for a claim), patients were required to have at least one prescription record of ART. ART was defined as a prescription for any of the following antiretroviral drugs: NRTIs, NNRTIs, PIs, INSTIs, or EIs.

Data of patients meeting these criteria (n=28,089) during the study period were extracted from the database. Patients who had received first prescriptions for an ART regimen between 2011 and 2019 (n=16,069) were included in the present analysis.

Outcomes

Primary outcomes were switch rates and time-to-switch associated with individual ART regimens by anchor drug classes. Secondary outcomes were switch rates and time-to-switch associated with anchor drug class-based ART regimens by type of backbone drug, characteristics of patients who experienced an anchor drug switch in each anchor drug class-based ART regimen, and common switching patterns of anchor drug classes.

Definitions

Data extracted from the NDB included patients' demographic characteristics (age, sex), and clinical characteristics, including year of first ART record in the database, prescription records of anchor drugs and backbone drugs, comorbidities, hospitalization history, and AIDS-defining illnesses.

Anchor drugs and backbone drugs

The anchor drugs of the ART regimens were identified using receipt codes and were classified into three anchor drug classes according to the anti-HIV drug classification available in Japan:[3] 1) NNRTIs, 2) PIs, or 3) INSTIs.

The backbone drugs of the ART regimens were identified using receipt codes and classified into four categories: 1) tenofovir disoproxil fumarate (TDF); 2) abacavir (ABC); 3) tenofovir alafenamide fumarate (TAF); and 4) others.

ART regimen switch and time-to-switch

An ART regimen switch involved only anchor drug classes and was defined on the basis of a switch in the specific anchor drug class used in the ART regimen. The time-to-switch of an ART regimen was defined as the period from the date of the first record of anchor drug class in the ART regimen (defined as the first regimen) recorded within patient data (index date) to the date of switching to another anchor drug class in the subsequent ART regimen (defined as the second regimen) during the study period. The date of an anchor drug class switch was defined as the date of prescription of the new anchor drug class after the termination of the preceding (first) ART regimen. A regimen was considered discontinued when no

initiation of any new anchor drug class was identified after termination of the preceding (first) ART regimen. A change of anchor drug within the same anchor drug class was not considered a switch.

AIDS-defining illnesses

AIDS-defining illnesses were identified by the presence of any of the following records prior to index date: HIV non-tuberculous mycobacteria, HIV cytomegalovirus infection, HIV candidiasis, HIV *Pneumocystis carinii* pneumonia, HIV Kaposi's sarcoma, HIV Burkitt's lymphoma, HIV non-Hodgkin's lymphoma, HIV encephalopathy, HIV-associated dementia, slim disease, acquired immune deficiency syndrome, AIDS, neonatal HIV infection, and AIDS-related complex. The corresponding ICD-10 codes are listed in Supplementary Table 1.

Comorbidities

Comorbidities were identified if any ICD-10-coded chronic illnesses were present prior to the index date, including: HIV-related diseases, hypertension, dyslipidemia, hepatitis B/C coinfection, diabetes mellitus, bone disorder, vascular disease, psychiatric disorders, kidney disease, malignancy, and syphilis. Corresponding ICD-10 codes are listed in Supplementary Table 1.

History of hospitalization

A history of hospitalization was identified if a record of hospitalization was present before the ART regimen was prescribed.

Statistical analysis

The proportions of anchor drug class-based and backbone-based drugs prescribed on the index date were obtained by year. Demographic and clinical characteristics of all patients on ART regimens were analyzed descriptively according to the anchor drug class prescribed on the index date. The median time-to-switch and switch rates according to anchor drug class prescribed on the index date and those stratified by the backbone drugs were estimated using Kaplan-Meier analysis. To estimate 95% confidence interval (CIs), the Brookmeyer and Crowley method was used for the median number of days, and the Greenwood method was used for switch rates. Log-rank tests were used to compare switch rates between the respective drug classes in each year. The Bonferroni method was performed to adjust p-values on multiple comparison. Discontinuation or continuation of the regimen to the end of the study period was censored.

The demographic and clinical characteristics of patients who switched anchor drug classes in their ART regimens were analyzed descriptively according to the anchor drug class prescribed on the index date. Timings of <1 and ≥1 year were analyzed descriptively for patients who switched anchor drug classes in their ART regimens according to the anchor drug class prescribed on the index date and the corresponding 95% CI using Wilson scores.

Confounding factors for switching ART regimens and factors interacting with the anchor drug class were selected a priori based on previous studies. Time-to-switch was an objective variable and the anchor drug class, risk factors, and interaction term between anchor drug classes and each risk factor were included as explanatory variables in this model. The hazard ratio (HR) of each anchor drug class was calculated after adjusting for remaining variables and stratified by interaction factors to estimate the risk of switching anchor drug classes from the ART regimen prescribed on the index date.

All statistical analyses were performed in the R 4.0.3 environment (R Core Team, 2020). All remaining statistical tests were two-sided, and $p < 0{\cdot}05$ indicated significance.

Results

Patient disposition

A total of 28,089 patients in the database had a coded diagnostic record of HIV during the study period. Of these, 27,912 were prescribed anchor drugs. After excluding 866 patients for whom multiple anchor drug classes were prescribed on the index date and patients with prescription records of EI as the first anchor drug, 27,046 patients had a single prescription record of an anchor drug class on the index date. Broad use of the INSTI class in the database started after 2010, two years after INSTIs were introduced in Japan in July 2008. Therefore, the main results reported in the present study are derived from patients who started an ART regimen between 2011 and 2019 (n = 16,069) (Supplementary Figure 1).

Distribution of anchor drug class and backbone drugs in ART regimens by year

Prescriptions for NNRTIs and PIs as anchor drug classes in overall ART regimens decreased after 2011 (NNRTIs: 18%–1% from 2011 to 2019; PIs: 52%–4% from 2011 to 2019) (Fig. 1a). Contrary to these trends, prescriptions for INSTIs increased rapidly since 2011 and accounted for the majority of anchor drug classes prescribed in 2019 (30% in 2011 and 95% in 2019). Among backbone drug types, changes were observed starting from 2016. TDF was the predominant backbone drug type between 2011 and 2016 (80%–50%), followed by ABC (14% in 2011 to 38% in 2016) (Fig. 1b). TAF was the predominant backbone drug type from 2017 to 2019 (55% in 2017 to 70% in 2019).

Of 16,069 patients who started an ART regimen during 2011–2019, 7·5% (n = 1,204) were on NNRTIs, 24.3% (n= 3,901) on PIs, and 68·2% (n = 10,964) on INSTIs (Supplementary Table 2). Patients on INSTIs had higher proportions of psychiatric disorders compared to patients on NNRTIs and PIs (Supplementary Table 2).

Characteristics of patients who switched anchor drug classes

Of all patients who started an ART regimen from 2011 to 2019, 19·3% (3,108 patients) switched anchor drug classes. For each anchor drug class, 47·1% switched from NNRTIs (568/1,204), 52·7% from PIs (2,057/3,901), and 4·4% from INSTIs (483/10,964) (Table 1). No significant differences were found in patients' characteristics between those treated with these three predominant anchor drug classes. AIDS-

defining illnesses were present in 60·5% of patients treated initially with INSTIs, whereas the proportions were lower in those treated initially with NNRTIs or PIs (51·4% and 50·9%, respectively). The proportion of patients with vascular diseases was highest among patients treated initially with INSTIs (8·3%) compared to those treated initially with NNRTIs (4·4%) or PIs (3·5%). The proportion of patients with psychiatric disorders was highest among patients treated initially with INSTIs (27·3%), followed by those with PIs (16·4%) and NNRTIs (14·6%) (Table 1).

Switching patterns of anchor drug classes

Of the 3,108 patients who switched anchor drug classes from their first to second ART regimens (Fig. 1c), most patients treated initially with NNRTIs and PIs switched to INSTIs (67·3% [95% CI: 63·9%–70·4%] and 85·9% [84·4%–87·3%], respectively) <1 year after starting the first regimen; 65·6% [95% CI: 63·1%–68·0%) of patients treated initially with INSTIs switched to PIs in the second regimen. Of the patients who switched their anchor drug class ≥1 year after starting their first regimen, most of those treated initially with NNRTIs and PIs switched to INSTIs (95·5%, [95% CI: 94·4%–96·3%] and 93·6% [95% CI: 93·0%–94·1%], respectively), whereas of those treated initially with INSTIs, 55·4% [95% CI: 52·0%–58·8%] switched to PIs.

Switching of anchor drug classes in the ART regimens

The switch rates for both NNRTIs and PIs increased constantly over eight years (from 14·9% to 65·5% and 13·2% to 67·7%, respectively), whereas patients taking INSTIs maintained a low switch rate (from 3·0% to 7·6%) (Fig. 2). NNRTIs and PIs had median time-to-switch of 1,826 and 1,583 days, respectively, but INSTIs had a low switch rate of 7·6% at eight years, so time-to-switch could not be obtained. Log-rank tests showed significant differences in switch rates of any pairs of anchor drug classes at years one through eight (all $p < 0·05$).

Switching of anchor drug class-based backbone drugs in the ART regimens

In patients receiving NNRTIs, the switch rates at one year varied between backbone drugs, with the lowest rate in ABC backbone drugs (14·0%). In patients receiving PIs, the lowest rate was for TDF backbone drugs (10·7%) (Fig. 3). In the PI group, significant differences were found in the switching rates between TDF and ABC and between TDF and other backbone drugs (all $p <0·05$). In the INSTI group, equally low switch rates were observed at one year for TAF (2·1%), ABC (2·8%), and TDF (3·2%). The switch rate for TAF was slightly lower than for TDF and ABC; the highest switch rate was using other backbone drugs (9·4%).

Assessment of potential confounding factors associated with regimen switch

AIDS-defining illness, backbone type, and anchor drug class, and interaction terms between anchor drug class and AIDS-defining illness and between anchor drug class and type of backbone were selected for inclusion in the Cox regression analysis model. Subsequently, HRs were calculated for anchor drug class stratified by each interaction term with anchor drug class (AIDS-defining illness and backbone types). The

HRs were consistently higher in regimens with PIs and NNRTIs compared with those with INSTIs, regardless of the presence of AIDS-defining illness (HRs 7·70–9·06 for presence of AIDS, 13·07–13·14 for non-AIDS) or backbone type (HRs 11·39–11·78 for TAF, 10·84–11·05 for TDF, and 9·33–14·25 for ABC) (Fig. 4).

Discussion

The present study is the first to use the cross-sectional, nationwide Japanese NDB to analyze treatment data of HIV-positive Japanese persons. Analyses of switch rates, time-to-switch, and switching patterns of anchor drug classes of ART regimens showed that the most common switching pattern of anchor drug class was from NNRTIs or PIs to INSTIs. Switch rates for NNRTIs and PIs increased continuously over eight years, whereas initial INSTI regimens maintained low switch rates, validating the results of our preliminary study.[13]

Among PLWH enrolled in the present study, INSTI was the anchor drug class prescribed most frequently, and TAF agents (about two-thirds of backbone prescriptions) were the predominant initial ART regimen of the latest 3 years. The 2017 HIV treatment guidelines published in Japan[17] reinforced these trends for initial ART regimens, showing that prescriptions for INSTI agents (e.g., raltegravir [RAL] and dolutegravir [DTG]) as initial anchor drug classes increased between 2012 and 2016; TDF was prescribed most frequently as a backbone drug followed by ABC in the same timeframe. There were some concerns regarding switching of backbone drugs in the literature; PLWH who switched from a TDF-based to a TAF-based cART regimen showed increased low-density lipoprotein (LDL) values exceeding their cardiovascular risk targets.[18,19] In the present study, equally low switch rates were observed at one year for TAF, ABC, and TDF. However, the true impact of TAF on lipid profiles or cardiovascular risk was not evaluated and requires further study.

Over the eight-year study period, the switch rates of anchor drug classes NNRTIs and PIs increased steadily. Switching anchor drug class also increased 20% over three years in Europe and the United States in treatment-naïve PLWH treated initially with both NNRTIs and PIs.[12] The majority of patients in the present study who were treated initially with NNRTIs and PIs switched to INSTIs regardless of switching times and/or backbone drugs, with low switch rates thereafter. These findings and similar findings reported by other investigators[20–22] suggest that INSTIs may be the most durable anchor drug class for PLWH on ART regimens, regardless of backbone drugs in the first ART regimen. Analysis of a large dataset of HIV-positive patients confirmed that initial INSTI-based regimens combined with TDF, TAF, or ABC were all potent and well tolerated without significant virological failure; only a small percentage of patients (12%) discontinued INSTI regimens, and DTG showed the lowest risk of virological failure.[23] The durability and efficacy of DTG were also reported in patients who switched to INSTI-based regimens, and subsequent switches were less likely than with RAL.[22] Switching regimens appears to be more stable in virologically suppressed HIV-1-infected patients who receive INSTI-based regimens initially.[21,24]

Other possible explanations suggested for increased switching include the expansion of HIV/AIDS treatment programs in middle-income or resource-limited areas.[25] In addition, HIV-infected patients are more likely to be younger, less educated, and to have detectable HIV-1 DNA when switching to a second-line cART regimen, which may predispose to worse outcomes. Comparison of outcomes of second-line cART regimens between 1996–1998 and 2008–2010 reported that failure rates decreased as time progressed and were independent of the cART regimen; risk of virologic failure of second-line cART was also lower in patients who had undetectable HIV-1 DNA at the time of switching.[26] Increases in ART drug resistance may also explain multiple switches in treatment.[27]

Of comorbidities, the prevalence of AIDS-defining illnesses was the highest in those treated initially with INSTIs, whereas dyslipidemia and diabetes mellitus prevalence was higher among patients receiving NNRTIs. Multivariate analysis, after adjusting for confounders, showed that the risk of switching anchor drug classes was lower in patients prescribed INSTIs, regardless of the presence of AIDS-defining illness or type of backbone prescribed, supporting long-term continuation of INSTIs prescribed for the first ART regimen.

Limitations

The present study has several limitations, including its cross-sectional design and retrospective analysis, which both limit inferences of causality. The study population was confined to Japan, and thus the results cannot be generalized to other populations. Furthermore, patients with more comorbid chronic illnesses or more complications of HIV infection may have been hospitalized in HIV-specialized institutions or institutions offering advanced medical care, which may limit generalizing results to all PLWH throughout Japan. Data were from an administrative database and certain clinical data from individual patients (e.g., adverse events, treatment failure, poor adherence) may be unavailable to accurately determine ART regimen changes or drug selection. A prospective long-term study is needed to confirm the durability of INSTIs as initial ART regimen drugs.

Conclusions

This is the first report of switch rates and time-to-switch of ART regimens using a NDB, which not only contains information on the largest number of HIV-positive patients in Japan, but also is representative of the entire population in Japan. The foremost switching strategies for first-to-second ART regimens were from NNRTIs or PIs to INSTIs. Incorporating INSTIs as the anchor drugs in initial ART regimens maintains low switch rates for long durations, suggesting that INSTIs may be the most durable anchor drug class for PLWH on ART regimens, regardless of AIDS-defining illnesses or backbone drug types prescribed.

Declarations

Sources of Funding

This work was supported by the Ministry of Health, Labour and Welfare (MHLW) Research on HIV/AIDS Program Grant Number JPMH20HB2001. However, this research has no conflict of interest.

Authors' contributions

TN, KF, and SF contributed to the study design. MY, NF, and ST contributed to the analysis and interpretation of the data. TN and SF had verified the underlying data. TN, HM, MS, KGH, and RK critically revised the draft manuscript and approved the final version of the manuscript for publication.

Declaration of interests

There are no conflicts of interest.

Funding: This work was supported by Ministry of Health, Labor and Welfare Research on HIV/AIDS Program Grant Number JPMH20HB2001.

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Tables

Table 1. Characteristics of patients who switched anchor drug class from the first ART regimen (n = 3,108)

Characteristic	Overall N = 3,108	NNRTI N = 568	PI N = 2,057	INSTI N = 483
Age group (years)				
< 20	- -	- -	- -	- -
20-29	153 (4.9%)	25 (4.4%)	89 (4.3%)	39 (8.1%)
30-39	836 (26.9%)	146 (25.7%)	574 (27.9%)	116 (24.0%)
40-49	1,142 (36.7%)	204 (35.9%)	773 (37.6%)	165 (34.2%)
50-59	603 (19.4%)	116 (20.4%)	398 (19.3%)	89 (18.4%)
60-69	264 (8.5%)	57 (10.0%)	160 (7.8%)	47 (9.7%)
≥ 70	about 100 -	about 10 -	about 60 -	about 20 -
Sex				
Male	2,855 (91.9%)	529 (93.1%)	1,883 (91.5%)	443 (91.7%)
Female	253 (8.1%)	39 (6.9%)	174 (8.5%)	40 (8.3%)
AIDS-defining illness	1,632 (52.5%)	292 (51.4%)	1,048 (50.9%)	292 (60.5%)
Diabetes	739 (23.8%)	120 (21.1%)	490 (23.8%)	129 (26.7%)
Dyslipidemia	577 (18.6%)	87 (15.3%)	398 (19.3%)	92 (19.0%)
Hypertension	328 (10.6%)	65 (11.4%)	185 (9.0%)	78 (16.1%)
Bone disorder	78 (2.5%)	- -	52 (2.5%)	about 10 -
Vasculer diseases	138 (4.4%)	25 (4.4%)	73 (3.5%)	40 (8.3%)
Angina	74 (2.4%)	15 (2.6%)	36 (1.8%)	23 (4.8%)
Stroke	62 (2.0%)	- -	39 (1.9%)	about 10 -
Myocardial infraction	- -	- -	- -	- -
Kidney disease	133 (4.3%)	22 (3.9%)	75 (3.6%)	36 (7.5%)
Urolithiasis	86 (2.8%)	16 (2.8%)	46 (2.2%)	24 (5.0%)
Chronic kidney disease	49 (1.6%)	- -	29 (1.4%)	about 10 -
Cancers	268 (8.6%)	39 (6.9%)	150 (7.3%)	79 (16.4%)
AIDS-delining cancers	188 (6.0%)	27 (4.8%)	102 (5.0%)	59 (12.2%)
Non-AIDS-delining cancers	103 (3.3%)	17 (3.0%)	57 (2.8%)	29 (6.0%)
Psychiatric disorders	553 (17.8%)	83 (14.6%)	338 (16.4%)	132 (27.3%)
Mania and Depression	356 (11.5%)	47 (8.3%)	219 (10.6%)	90 (18.6%)
Anxious	260 (8.4%)	42 (7.4%)	155 (7.5%)	63 (13.0%)
Psychosis	113 (3.6%)	13 (2.3%)	71 (3.5%)	29 (6.0%)
Insomnia	15 (0.5%)	- -	- -	- -
Dementia	- -	- -	- -	- -
Hepatitis B infection	343 (11.0%)	60 (10.6%)	231 (11.2%)	52 (10.8%)
Hepatitis C infection	221 (7.1%)	36 (6.3%)	141 (6.9%)	44 (9.1%)
Syphilis	939 (30.2%)	150 (26.4%)	635 (30.9%)	154 (31.9%)
Hospitalize				
Hospitalized	1436 (46.2%)	220 (38.7%)	924 (44.9%)	292 (60.5%)
Never	1672 (53.8%)	348 (61.3%)	1,133 (55.1%)	191 (39.5%)
Year of ART initiation				
2011	844 (27.2%)	196 (34.5%)	564 (27.4%)	84 (17.4%)
2012	837 (26.9%)	137 (24.1%)	637 (31.0%)	63 (13.0%)
2013	671 (21.6%)	120 (21.1%)	488 (23.7%)	63 (13.0%)
2014	351 (11.3%)	64 (11.3%)	202 (9.8%)	85 (17.6%)
2015	167 (5.4%)	22 (3.9%)	75 (3.6%)	70 (14.5%)
2016	110 (3.5%)	15 (2.6%)	43 (2.1%)	52 (10.8%)
2017	81 (2.6%)	- -	about 20 -	43 (8.9%)
2018	about 40 -	- -	about 10 -	about 20 -
2019	- -	- -	- -	- -

Excluded "non-switcher" from Supplement Table 2)

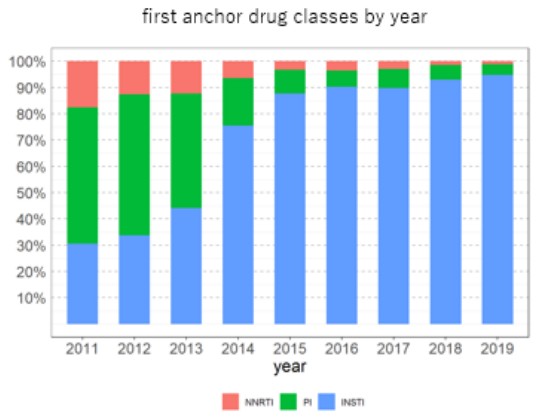
ART: antiretroviral therapy, NNRTI: non-nucleoside reverse transcriptase inhibitor, PI: protease inhibitor, INSTI: integrase strand transfer inhibitor
Values are expressed as number (percentage) unless specified otherwise.

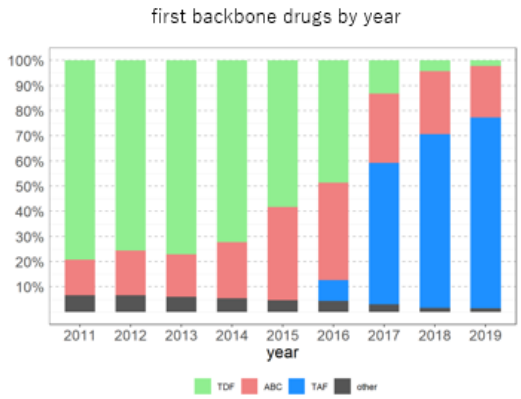
Supplement Table 1. ICD-10 codes used to identify AIDS-defining illnesses and comorbidities

Disease name	ICD-10 code
AIDS-defining illnesses	
HIV non-tuberculous mycobacteria	B20.0
HIV cytomegalovirus infection	B20.2
HIV other viral infections	B20.3
HIV candidiasis	B20.4
HIV Pneumocystis carinii pneumonia	B20.6
HIV Kaposi's sarcoma	B21.0
HIV Burkitt's lymphoma	B21.1
HIV non-Hodgkin's lymphoma	B21.2
HIV encephalopathy	B22.0
HIV lymphoid interstitial pneumonitis	B22.1
Slim disease	B22.2
HIV other specified conditions	B23.8
AIDS	B24
AIDS-related complex	B24
Malignant neoplasm of the cervix uteri	C53
AIDS-defining cancers	
Kaposi sarcoma	B21.0, C46
Burkitt lymphoma	B21.1, C83.7
Non-Hodgkin lymphoma	B21.2, C82-C85
Malignant neoplasm of the cervix uteri	C53
Non-AIDS-defining cancers	
Cancer other than the above	C00-97 (exclude C46, C53, C82-C85, C83.7)
Comorbidities	
HIV-related diseases	-
Cytomegaloviral disease	B25, B45, B59, C46.9, C81
Hypertension	I10, I12, I14–15
Dyslipidemia	-
Hypercholesterolaemia or hyperlipidaemia	E78.0–78.5
Hepatitis B infection	B18.1
Hepatitis C infection	B18.2
Diabetes	-
Type 2 diabetes	E11–14
Bone disorder	-
Osteoporosis	M80–81
Vascular disease	-
Myocardial infarction	I21–22
Stroke	I64 and related receipt diagnosis codes
Angina pectoris	I20
Hypertensive heart and renal diseases	I11, I13
Psychiatric disorders	-
Mania and depression	F30–32
Anxiety	F40–41
Psychosis	F20–29
Dementia	F01, F03
Insomnia	F51
Kidney disease	-
Chronic kidney disease	N18–19
Urolithiasis	N20–21
Malignancies	B21.0-21.2, C00–97
Syphilis	A53

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

Figures



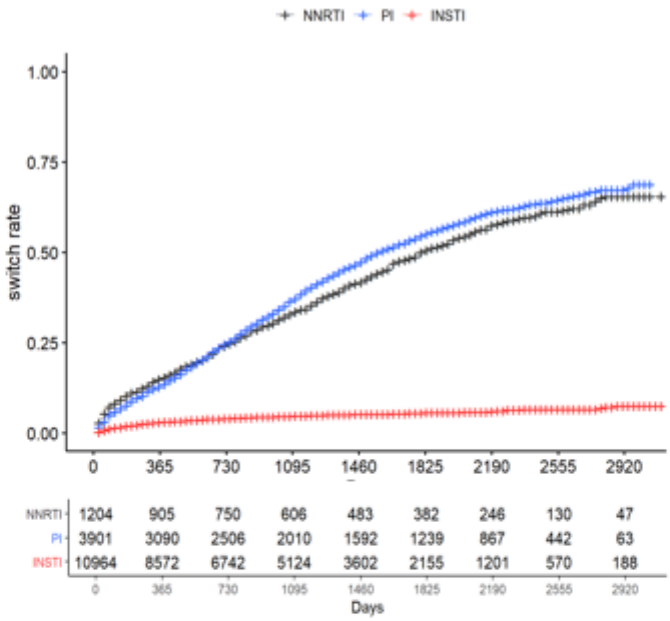


Timing of switch (n=3108)	Anchor drug class in the second regimen																	
	Switch < 1 year after starting the first regimen									Switch ≧ 1 year after starting the first regimen								
Anchor drug class in the first	NNRTI			PI			INSTI			NNRTI			PI			INSTI		
	n	%	(95%CI)	n	%	(95%CI)	n	%	(95%CI)	n	%	(95%CI)	n	%	(95%CI)	n	%	(95%CI)
NNRTI	-	-	-	56	(32.7%)	(29.6 -36.1)	115	(67.3%)	(63.9 -70.4)	-	-	-	17	(4.3%)	(3.4 -5.3)	379	(95.5%)	(94.4 -96.3)
PI	61	(12.5%)	(11.2 -13.9)	-	-	-	420	(85.9%)	(84.4 -87.3)	87	(5.5%)	(5.0 -6.1)	-	-	-	1467	(93.6%)	(93.0 -94.1)
INSTI	88	(28.6%)	(26.3 -31.0)	202	(65.6%)	(63.1 -68.0)	-	-	-	62	(35.4%)	(32.2 -38.8)	97	(55.4%)	(52.0 -58.8)	-	-	-

The number of cases includes patients for whom EI was prescribed as the second anchor drug, however, it is omitted due to low numbers.

Figure 1

Distribution of (a) anchor and (b) backbones drug classes prescribed in first ART regimen by year (2011-2019) (n = 16,069)

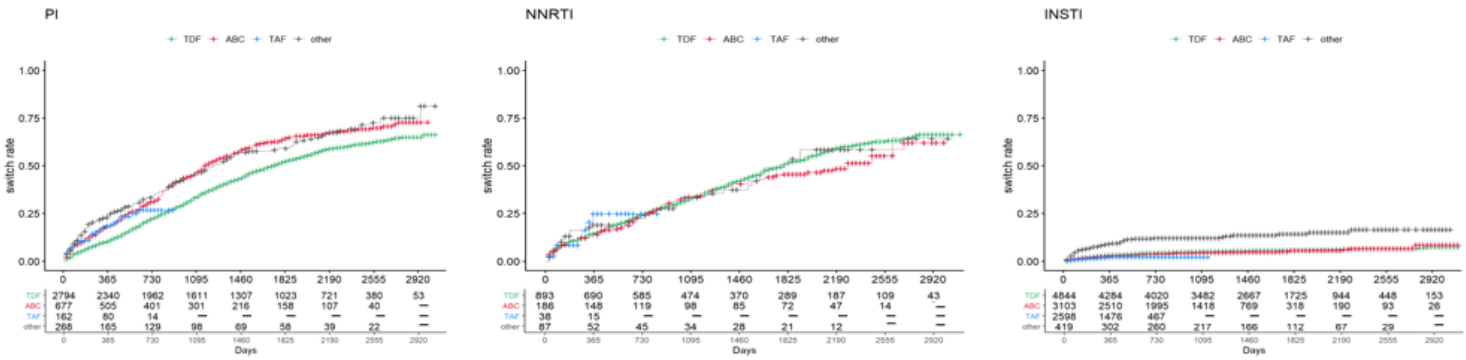


Anchor drug class	Regimen switch	Discontinued/censored	Median time-to-switch (days)		Switch rate at 1 year			Switch rate at 2 years			Switch rate at 3 years			Switch rate at 4 years		
	n	n	Days	(95%CI)	Rate	(95%CI)	Days from regimen initiation	Rate	(95%CI)	Days from regimen initiation	Rate	(95%CI)	Days from regimen initiation	Rate	(95%CI)	Days from regimen initiation
NNRTI	636	568	1826	(1674 -1980)	0.140	(0.128 -0.170)	360	0.246	(0.220 -0.271)	731	0.329	(0.300 -0.357)	1095	0.416	(0.384 -0.446)	1461
PI	1844	2057	1583	(1521 -1675)	0.132	(0.121 -0.143)	365	0.240	(0.235 -0.263)	730	0.366	(0.349 -0.381)	1095	0.470	(0.452 -0.486)	1461
INSTI	10481	483	NA	NA NA	0.030	(0.027 -0.034)	365	0.041	(0.037 -0.045)	730	0.047	(0.043 -0.052)	1095	0.053	(0.048 -0.058)	1461

	Switch rate at 5 year			Switch rate at 6 years			Switch rate at 7 years			Switch rate at 8 years		
	Rate	(95%CI)	Days from regimen initiation	Rate	(95%CI)	Days from regimen initiation	Rate	(95%CI)	Days from regimen initiation	Rate	(95%CI)	Days from regimen initiation
	0.501	(0.467 -0.532)	1826	0.575	(0.540 -0.607)	2190	0.616	(0.579 -0.650)	2580	0.655	(0.613 -0.692)	2920
	0.547	(0.529 -0.564)	1826	0.611	(0.593 -0.628)	2190	0.645	(0.626 -0.662)	2550	0.677	(0.655 -0.698)	2940
	0.057	(0.051 -0.062)	1830	0.060	(0.054 -0.066)	2190	0.066	(0.059 -0.074)	2370	0.076	(0.063 -0.089)	2863

Figure 2

Time-to-switch of ART regimens according to anchor drug class from 2011–2019



Anchor drug class	Backbone	Regimen switch n	Discontinued/censored n	Median time-to-switch (days) Days	(95%CI)	Switch rate at 1 year Rate	(95%CI)	P-value		Days from regimen initiation
NNRTI										
	TDF	448	445	1795	(1650 -1979)	0.145	(0.121 -0.169)	TDF vs ABC	1	360
	ABC	104	82	2280	(1584 -NA)	0.140	(0.087 -0.189)	TDF vs TAF	1	360
	TAF	31	-	NA	NA NA	0.249	(0.065 -0.337)	TDF vs others	1	360
	others	53	34	1736	(1523 -NA)	0.191	(0.095 -0.277)	ABC vs TAF	1	335
								ABC vs others	1	
								TAF vs others	1	
PI										
	TDF	1306	1488	1740	(1650 -1827)	0.107	(0.095 -0.118)	TDF vs ABC	<0.05	365
	ABC	281	326	1170	(1096 -1300)	0.186	(0.156 -0.216)	TDF vs TAF	0.082	365
	TAF	130	32	NA	NA NA	0.187	(0.118 -0.251)	TDF vs others	<0.05	360
	others	127	141	1230	(1020 -1522)	0.235	(0.179 -0.287)	ABC vs TAF	1	365
								ABC vs others	1	
								TAF vs others	1	
INSTI										
	TDF	4585	259	NA	NA NA	0.032	(0.027 -0.037)	TDF vs ABC	1	365
	ABC	2977	126	NA	NA NA	0.028	(0.022 -0.034)	TDF vs TAF	0.002	366
	TAF	2550	48	NA	NA NA	0.021	(0.015 -0.027)	TDF vs others	<0.05	365
	others	393	50	NA	NA NA	0.094	(0.064 -0.123)	ABC vs TAF	0.004	366
								ABC vs others	<0.05	
								TAF vs others	<0.05	

Figure 3

Time-to-switch of ART regimens by anchor drug class-based backbone type from 2011–2019

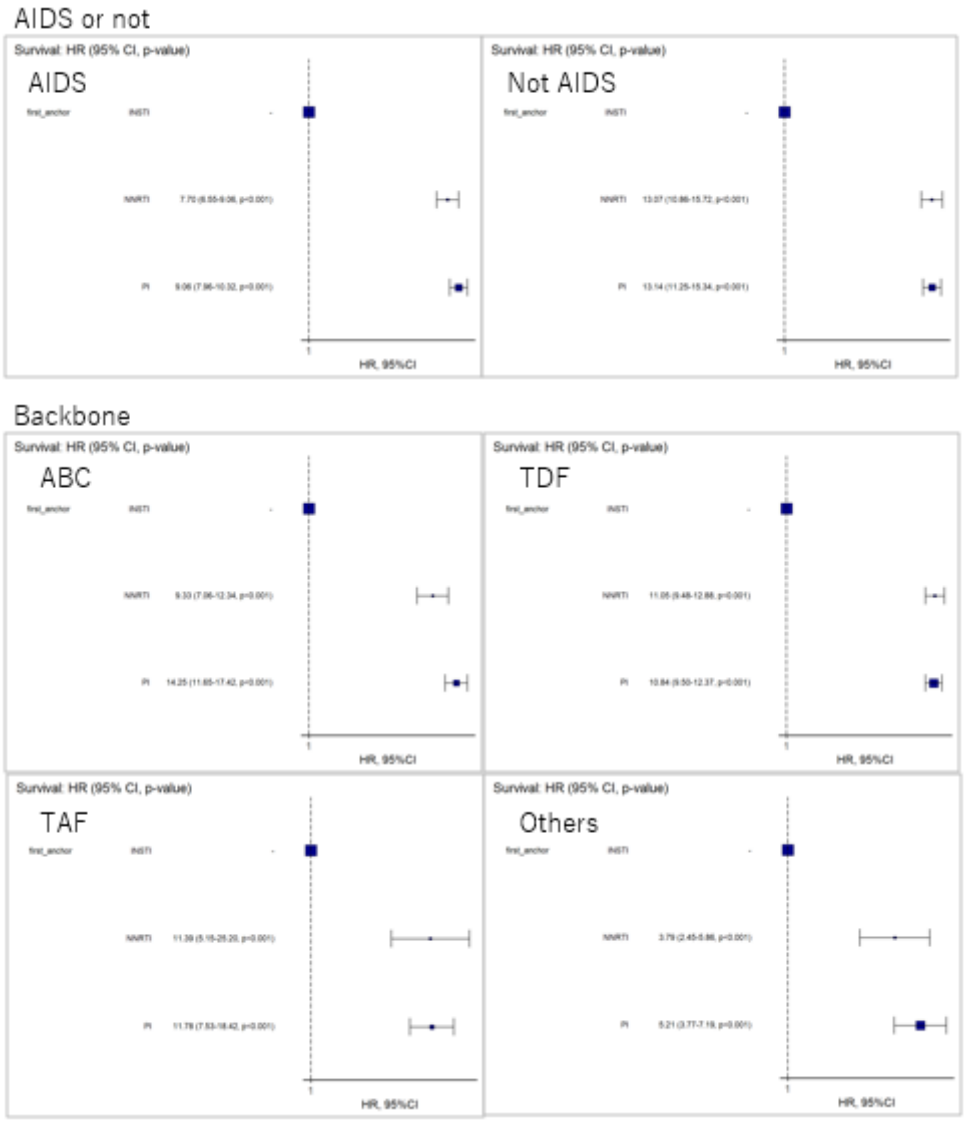


Figure 4

Hazard ratio for switching of each anchor drug class stratified by AIDS-defining illness and backbone drug.

Supplementary Files

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- Onlinefloatimage2.png
- Onlinefloatimage3.png
- SuppFig1.png