

Profiles of 2-Drug Regimen in People Living with HIV-1 in A Real World Setting: A Large-Scale Medical Claim Database Analysis in Japan

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Abstract

Background Regimen simplification to 2-drug antiretroviral therapy (2-ART) may address potential tolerability issues, increase adherence, and reduce toxicity and potential drug-drug-interactions among people living with HIV-1 (PLWH). However, real-world treatment patterns and patient profiles associated with 2-ART are unclear.

Methods This retrospective observational cohort study employed a large-scale medical claim database of Japanese hospitals to extract data on 4,293 PLWH aged ≥ 18 years with diagnosis of HIV and treated with any ART regimens between April 2008 and April 2019. A 2-ART cohort was compared with a 3-drug antiretroviral therapy (3-ART) cohort in terms of patient characteristics, comorbid conditions, and treatment patterns. Treatment switching rates were calculated for each cohort followed by sensitivity analysis to confirm the robustness of the findings.

Results There were 94 patients identified in the 2-ART cohort. Compared to the standard 3-ART cohort ($n=3,993$), the 2-ART cohort was older (mean age 54.4 vs 43.4 years), with a lower proportion of males (87.2% vs 93.8%), higher Charlson Comorbidity Index (CCI) (mean score 6.9 vs 5.3), more co-medications (mean 8.3 vs 5.0), and a higher percentage of AIDS-defining conditions (66.0% vs 42.8%). The most common 2-ART were protease inhibitor (PI) + integrase strand transfer inhibitor (INSTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) + INSTI (33.0% and 31.9%, respectively). Overall, most of the regimens were nucleoside reverse transcriptase inhibitor (NRTI)-sparing (71.3%), with a decreasing trend over time (76.2% to 70.2%). ART regimen switch occurred more often in the 2-ART cohort than in the 3-ART cohort (33.0% vs 21.2%).

Conclusion The profiles of patients on 2-ART in Japan were demonstrated to be complex. Most patients were treated with NRTI-sparing regimens which may reflect an effort to reduce treatment-related toxicities.

Introduction

Antiretroviral therapy (ART) regimens have been credited with increasing the survival of people living with HIV-1 (PLWH) [1]. Three-drug ART regimens (3-ART), which consist of a backbone with two nucleoside reverse transcriptase inhibitors (NRTIs) plus an anchor drug with or without a booster, have become the standard of care (SoC) and treatment for HIV-1 infection [2, 3]. While advances in ART have been credited with improving survival by decades [4, 5], recent evidence of long-term adverse events (AEs) with 3-ART have been documented [6], particularly in terms of renal and bone toxicity [7–10]. Such poor outcomes have prompted development of drug-sparing strategies with a simplified 2-drug ART regimen (2-ART) in attempt to reduce its negative impact.

In contrast, multi-center clinical trials of 2-ART (dolutegravir plus lamivudine and dolutegravir plus rilpivirine) have demonstrated to have non-inferior efficacy as well as safety compared to 3-ART [11, 12]. Based on the positive impact, there is an increasing diversity of therapies with a 2-drug combination of

integrase strand transfer inhibitors (INSTI) plus protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI). More ART regimens are being developed and used in real-world settings to tailor to the long-term complexities related to a patient's genetic background, treatment history, and comorbidities [13].

In Japan, ART treatment uptake and clinical success among diagnosed HIV patients, in terms of viral suppression, has been shown to be excellent and in line with UNAIDS/WHO targets of 90% [3, 14, 15]. However, Japanese PLWH have been demonstrated to have unique comorbidities and co-medication patterns [16]. There is limited evidence that switching to 2-ART may improve outcomes [17]. While the practice of regimen switching and reduction is an increasing global trend, the profile and number of patients receiving 2-ART in real-world practice are not well understood in Japan. This study aimed to characterize patients who received 2-ART and provide an overview of ART treatment patterns in Japan.

Methods

Study design and data source

This study was a retrospective cohort analysis of ART treatment patterns and patient characteristics among adult patients living with HIV on 2-ART compared to 3-ART in Japan. Data were extracted from a hospital-based medical claims database maintained by Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan). The data is from all hospitals included in the MDV hospital panel, which covers 374 acute phase hospitals across regions (approximately 22% of acute phase hospitals in Japan) and roughly 25 million people. The MDV database includes treatment information, including antiretrovirals used, co-medications, and comorbidities, etc., but no laboratory results such as CD4 counts or plasma viral load.

Study Population

PLWH were included in the analyses if they had a diagnosis of HIV (ICD-10: B20-B24), had been treated with 2- or 3-ART, and were aged ≥ 18 years. The patient identification period for treatment index dates was from the first date available in the database (April 2008) to the last available (April 2019). A patient was considered to be on a 2-ART if they were prescribed any two antiretrovirals on the same day, and the first date of their 2-ART was the index date for this cohort. Patients who did not have any 2-ART during their patient record were eligible for the 3-ART cohort if they were prescribed three antiretrovirals on the same day. The first date of their 3-ART was considered to be the index date for this cohort. Patients were excluded if they were treated with a C-C chemokine receptor type 5 (CCR5) antagonist or two antiretrovirals in the same class as their index 2-ART because they are not SoC. Additionally, patients treated with any regimens outside of 1) INSTI + 2NRTI, 2) PI + 2NRTI, or 3) NNRTI + 2NRTI during their index 3-ART were excluded as they are also not SoC.

Demographic and clinical characteristics for the 2-ART cohort were stratified by three time periods to assess possible temporal changes due to novel drug access in Japan: April 1, 2008 to September 30,

2014 (representative of 1st generation INSTI availability, mainly raltegravir), October 1, 2014 to June 30, 2016 (representative of 2nd generation INSTI availability, including dolutegravir), and July 1, 2016 to April 30, 2019 (last available data period, representative of tenofovir alafenamide (TAF) availability as a novel prodrug of tenofovir to reduce toxicities). All drug classes and combinations were also tabulated for all patients. The average gap (days) between 2-ART and the total average duration of treatment were calculated from regimen initiation to last ART prescription in the database. Time to index regimen for the 2-ART cohort was calculated as the time from patients' first ART (prior to 2-drug initiation) to their index date.

Outcomes

Patient profiles

The analyses compared patient characteristics on 2-ART with those with 3-ART. Patient profiles consisted of demographics (age at index, gender, year of index date), co-medications, and comorbidities (hemophilia, AIDS-defining conditions, modified Charlson Comorbidity Index (CCI)). Modified CCI is severity indicator which is able to predict one-year mortality among hospitalized patients by weighting 17 different comorbid conditions (e.g. myocardial infarction, congestive heart failure), and has been validated using Japanese data [18]. Additionally, all 2- and 3-drug combinations observed for each cohort were tabulated. These combinations were described by drug class: INSTI, PI, NNRTI, and NRTI. Regimens that did not contain any NRTIs were considered to be NRTI-sparing regimens in alignment with the definition of U.S. Department of Health and Human Services [19].

ART regimen switch

Two- and 3-ART switch patterns were also assessed. Patients were considered to have switched their drug regimen if they had any change to their index regimen, such as an addition, removal, or exchange of a drug. For patients on 3-ART, they cannot switch to a 2-ART at any point by definition, since any evidence of 2-ART in a patient's record would classify that patient in the 2-ART cohort. In order to capture true switches, regimen changes were only counted as switches if they lasted for more than 90 days. Both patients on 2- and 3-ART were considered to have switched even if they remained on the same number of drugs, as long as a change in any component of their regimen as present. Specific transitions were not considered switches: the same regimen with only tenofovir disoproxil fumarate (TDF) switched to TAF, the same regimen with changes in dosing, or the same regimen with an added/switched booster. Switch rate was defined as number of patients who switched divided by total person years. Total person-years for treatment-switches was time from index treatment initiation to the first treatment switch, whereas for patients who did not switch it was defined as time from the first treatment initiation to the last ART prescription during the study period. The switch rate and time-to-next-switch were calculated from the index date to the patient's next treatment switch, the last ART claim in the database or end of the study period. The switch rate observed in among both cohorts were compared.

Finally, a sensitivity analysis of switching was performed to ensure the robustness of treatment pattern findings. As described in Fig. 1, only patients on 2-ART with at least one antiretroviral drug prior to their index date and patients on 3-ART with at least 1 switch after their index date were included to ensure the assessment of treatment experienced patients. In addition, only patients with at least one year of follow-up data were included to ensure that potential switches could be captured in the data. In the switch sensitivity analyses, the switch index date was set to patient's first switch for the 3-ART cohort and the switch rate was calculated from the time of the first switch to their next switch.

Statistical Analysis

All statistical analysis was completed on SAS version 9.4 (SAS Institute Inc., Cary, USA). All descriptive data were presented as frequencies for categorical variables and mean (standard deviation [SD]) for continuous variables. Comparisons were made using the chi-square and t-tests, respectively. Time-to-first switch is presented using Kaplan-Meier curves and 95% confidence limits of the switch rate were calculated assuming a Poisson distribution.

Results

Study sample

For the study period between April 1, 2008 and April 30, 2019, a total of 8,813 patients with a diagnosis of HIV were identified; of these, data on 4,293 patients aged ≥ 18 years treated with any ART regimens were extracted and 4,087 patients met the inclusion criteria and were included in the analysis. Among the included patients, 94 (2.3%) patients received a 2-ART on their index date and were classified as the 2-ART cohort. There were 3,993 (97.7%) patients who received a 3-ART and were classified as the 3-ART cohort. Figure 2 illustrates the flow of patient inclusion. The median duration of follow-up was 712 days and 701 days in the 2-ART cohort and the 3-ART cohort, respectively.

Baseline And Clinical Overview

Of the 94 patients in the 2-ART cohort, the mean age was 54.4 years (SD 12.7 years) and 87.2% were male. In contrast, the 3-ART cohort was significantly younger with a mean age of 43.4 years (SD 11.7 years) and included significantly more males (93.8%). The proportion of patients having hemophilia was greater in the 2-ART cohort than in the 3-ART cohort (12.8% vs. 2.1%; $p < 0.0001$). (Table 1).

Table 1
Baseline characteristics

	2-Drug		3-Drug		P-value
Demographics (at Index)					
Age	94		3993		
Mean (SD)	54.40 (12.70)		43.40 (11.70)		< 0.0001
Median (Q1, Q3)	53 (44, 64)		42 (35, 50)		
Min, max	27,82		18,90		
Gender (n, %)					
Male	82	87.23%	3745	93.79%	0.0101
Female	12	12.77%	248	6.21%	
Hemophilia (n, %)					
Yes	12	12.77%	84	2.10%	< 0.0001
No	82	87.23%	3909	97.90%	
Year of index date (n, %)					
Cluster 1 (April 1, 2008- September 30, 2014)	21	22.34%	1057	26.47%	< 0.0001
Cluster 2 (October 1, 2014- June 30, 2016)	26	27.66%	420	10.52%	
Cluster 3 (July 1, 2016 - April 1, 2019)	47	50.00%	2516	63.01%	
Clinical background Summary					
Co-medications					
N with at least other 1 medication class	87	92.55%	2996	75.03%	< 0.0001
Mean (SD)	8.28 (6.71)		4.99 (4.61)		< 0.0001
Median (Q1, Q3)	6 (4, 11)		3 (2, 7)		
Min, max	1,34		1,42		

*Although all patients included in the analysis had an HIV diagnosis code, not all 3-drug patients had a diagnosis for HIV using the Charlson Comorbidity HIV codes; which does not include B23 (*HIV disease resulting in other conditions*), yet was used for the study population definition.

	2-Drug		3-Drug		P-value
AIDS-defining conditions					
N with at least 1 condition	62	65.96%	1708	42.77%	< 0.0001
Mean (SD)	1.74 (0.87)		1.77 (1.04)		0.8441
Median (Q1, Q3)	2 (1, 2)		1 (1, 2)		
Min, max	1,4		1,7		
Charlson Comorbidity Index					
Mean (SD)	6.85 (2.3)		5.32 (1.63)		< 0.0001
Median (Q1, Q3)	6 (5,8)		5 (4,6)		
Min, max	4,14		0,17		
Charlson comorbid conditions					
Congestive Heart failure	25	26.60%	202	5.06%	< 0.0001
Dementia	0	0.00%	17	0.43%	N/A
Chronic pulmonary disease	28	29.79%	940	23.54%	0.1592
Rheumatologic disease	4	4.26%	49	1.23%	0.0326
Mild liver disease	41	43.62%	1330	33.31%	0.0364
Diabetes with chronic complications	18	19.15%	163	4.08%	< 0.0001
Hemiplegia or paraplegia	2	2.13%	30	0.75%	0.1669
Renal disease	32	34.04%	192	4.81%	< 0.0001
Any malignancy, including lymphoma and leukemia	16	17.02%	294	7.36%	0.0005
Moderate or severe liver disease	5	5.32%	23	0.58%	0.0004
Metastatic solid tumor	2	2.13%	37	0.93%	0.2257
HIV	94	100.00%	3990	99.92%*	N/A

*Although all patients included in the analysis had an HIV diagnosis code, not all 3-drug patients had a diagnosis for HIV using the Charlson Comorbidity HIV codes; which does not include B23 (*HIV disease resulting in other conditions*), yet was used for the study population definition.

	2-Drug		3-Drug		P-value
Other relevant systemic diseases					
Hemodialysis (artificial kidney, chronic maintenance dialysis)	6	6.38%	6	0.15%	< 0.0001
Cardiovascular diseases	12	12.77%	178	4.46%	0.0012
Hypertension	50	53.19%	765	19.16%	< 0.0001
Lipid disorders	40	42.55%	711	17.81%	< 0.0001
Bone Disorders	17	18.09%	251	6.29%	< 0.0001
Peripheral Neuropathy	0	0.00%	0	0.00%	N/A
Any Diabetes	48	51.06%	871	21.81%	< 0.0001
Psychiatric disorders	39	41.49%	1446	36.21%	0.2931
Hepatitis B/C Co-Infection	24	25.53%	878	21.99%	0.4129
*Although all patients included in the analysis had an HIV diagnosis code, not all 3-drug patients had a diagnosis for HIV using the Charlson Comorbidity HIV codes; which does not include B23 (<i>HIV disease resulting in other conditions</i>), yet was used for the study population definition.					

Co-medications

Of patients in the 2-ART cohort, 92.6% had been prescribed at least one class of co-medication with a mean of 8.3 different co-medication classes (based on ATC level 4 code) during the follow-up period. The top five most common co-medication classes were proton pump inhibitors, angiotensin II antagonists, calcium antagonists, anti-gout preparations, and non-barbiturates and statins [see **Additional file 1**]. In contrast, 75.0% of patients in the 3-ART cohort have been prescribed a co-medication, with a lower mean number of different co-medication classes (5.0; $p < 0.0001$) [see **Additional file 2**]. The most commonly prescribed co-medications in the 3-ART cohort included systemic antihistamines, non-barbiturates, proton pump inhibitors, non-steroidal anti-rheumatics, and other anti-ulcerants.

Aids-defining Conditions And Comorbidities

AIDS-defining conditions varied between the 2- and 3-ART cohorts; 66.0% of patients on 2-ART had an AIDS-defining condition compared with 42.8% of those on 3-ART [see **Additional file 3**]. AIDS-defining conditions other than an AIDS diagnosis were present in 42.6% and 31.6% of the 2- and 3-ART cohorts,

respectively. A diagnostic code for AIDS itself was found in 52.1% and 24.8% of the 2- and 3-ART cohorts, respectively. The top 5 most common AIDS-defining conditions other than AIDS itself was the same for both cohorts: pneumocystis (20.2% and 22.1%), cytomegalovirus disease (17.0% and 10.5%), tuberculosis (6.4% and 6.4%), non-Hodgkins lymphoma (4.3% and 3.2%), and encephalopathy (4.3% and 2.5%).

Comorbidities

Nearly all Charlson comorbid conditions were more prevalent in the 2-ART cohort than in the 3-ART cohort (mean score 6.9 vs. 5.3), with the largest differences found for mild liver disease (43.6% vs. 33.3%), congestive heart failure (26.6% vs. 5.1%), renal disease (34.0% vs. 4.8%), diabetes with chronic complications (19.2% vs. 4.1%), and malignancies (17.0% vs. 7.4%) (Table 1). In addition, the 2-ART cohort also showed a significantly higher prevalence of all other relevant systemic diseases, except for psychiatric disorders and hepatitis B/C co-infection.

Treatment Patterns

Among patients on a 2-ART, NRTI-sparing regimens comprised the majority of all 2-ARTs (71.3%) (Fig. 3a). Overall, the most common class combinations for this cohort were PI + INSTI (33.0%) and NNRTI + INSTI (31.9%). Among patients treated with a 3-ART, the most common drug class combinations were INSTI + 2NRTI (66.6%), followed by PI + 2NRTI (20.5%) and NNRTI + 2NRTI (12.9%). The top common antiretroviral drug combinations for both cohorts are presented in **[Additional file 4]**.

The 2-ART cohort comprised of 1.9% of all patients from April 1, 2008 to September 30, 2014 (representative of 1st generation INSTI), 5.8% between October 1, 2014 and June 30, 2016 (representative of 2nd generation INSTI), and 1.8% between July 1, 2016 and April 30, 2019 (representative of TAF). Among patients in the 2-ART cohort, NRTI-sparing regimens were frequently found in all time periods examined (Fig. 3b). Within the 2-ART cohort, the first time period (April 1, 2008 to September 30, 2014) had the highest proportion of NRTI-sparing regimens (76.2%), with the proportion decreasing slightly to 69.2% in the second time period (October 1, 2014 to June 30, 2016), then leveling out at 70.2% in the last time period (July 1, 2016 to April 30, 2019). Over time, there was a shift in drug class among NRTI-sparing regimens among the 2-ART cohort. Specifically, PI + INSTI (61.9%) regimens were dominant in the first time period (April 1, 2008 to September 30, 2014), but NNRTI + INSTI regimens were most common from October 1, 2014 to April 30, 2019.

Switch Analyses

ART regimen switch occurred more often in the 2-ART cohort (33.0%; 31/94) than in the 3-ART cohort (21.2%; 845/3993). The switch rate was 20.88 switches/100 person-years (95% CI: 14.68–29.68) in the 2-

ART cohort, and 10.34 switches/100 person-years (95% CI: 9.66–11.06) in the 3-ART cohort; however, no statistical comparisons were made (Table 2). In the time-to-switch analysis, around 25% of patients in the 2-ART cohort had their first switch within one year, while only 10% of patients in the 3-ART cohort had their first switch within one year. As presented in the Kaplan-Meier curve, the higher switch rate in the 2-ART cohort was most evident prior to year 5 of follow-up. However, due to the small patient sample, long-term switch rates were more difficult to evaluate [see **Additional file 5**].

Table 2
Treatment switching patterns

	N	Switch rate (/100 person years)	Lower CI	Upper CI
Any Switch	876	10.52	9.85	11.24
2-Drug regimen cohort	31	20.88	14.68	29.68
2-Drug to 2-drug switches	3			
2-Drug to 3-drug switches	24			
2-Drug to 4-drug switches	4			
3-Drug regimen cohort	845	10.34	9.66	11.06
3-Drug to 3-drug switches	832			
3-Drug to 4-drug switches	9			
3-Drug to 1-drug switches	4			
<i>Switch sensitivity analyses*</i>				
Any Switch	130	6.43	5.42	7.64
2-Drug regimen cohort	19	29.24	18.65	45.84
2-Drug to 2-drug switches	2			
2-Drug to 3-drug switches	13			
2-Drug to 4-drug switches	4			
3-Drug regimen cohort**	111	5.67	4.71	6.83
3-Drug to 3-drug switches	107			
3-Drug to 4-drug switches	2			
3-Drug to 1-drug switches	2			
*subset of patients with at least 1 year follow-up and 1 prior switch				
**Only patients who additionally switched to another 3-drug regimen were included.				

Of all switches in the 2-ART cohort, 77.4% (24/31) was from 2-ART to 3-ART (Table 2). All switch patterns for the 2-ART cohort are presented in [Additional file 6]. The most common switching patterns were from PI + NRTI to PI + 2NRTI and PI + INSTI to INSTI + 2NRTI. Only 9.7% (3/31) of all switches in the 2-ART cohort were from a 2-ART to another 2-ART. In the 3-ART cohort, because patients could not switch to a 2-ART by definition, 98.5% (832/845) of all switches were to another 3-ART (rather than to a 1- or 4-drug regimen). The most prevalent switch pattern was from PI + 2NRTI to INSTI + 2NRTI. About 1% of 3-ART switching patients changed to a 4-drug regimen, such as adding a PI to INSTI + 2NRTI regimen.

Sensitivity analysis demonstrated that in the subset of patients with at least 1 year follow-up and 1 prior switch, the switch rate (per 100 person-years (PY)) was higher among the 2-ART cohort (29.24/PY; 95% CI: 18.65–45.84/PY) compared to the 3-ART cohort (5.67/PY; 95% CI: 4.71–6.83/PY).

Discussion

To our knowledge, this is the first study to assess the characteristics of PLWH on a 2-drug regimen, ART treatment patterns, and drug switching in Japan. This retrospective cohort study used over 10 years of hospital-based claim data described the patient characteristics and treatment pattern of 2-ART cohort compared with 3-ART cohort, and explored switching among 2- and 3-ART cohorts in a real-world setting. Despite the small proportion of 2-ART cohort identified, and 2-ART cohort were more experienced at the index date chosen for each cohort, patients on a 2-ART were significantly older, received a larger number of co-medications, and had a higher CCI score as well as higher proportion of patients with AIDS-defining conditions and hemophilia, compared with patients on a 3-ART.

These characteristics suggest that disease status were more severe and complicated in patients on a 2-ART. In addition, hypertension, diabetes, lipid disorders, renal disease and congestive heart failure were more common and significantly higher in the 2-ART cohort compared with 3-ART cohort. Similar comorbidities were highlighted in a review of multi-comorbidities in PLWH [20]. The authors also proposed clinical reassessment schedules for at-risk patients, defined as those who are older than 50 years, have 2 or more comorbidities or receiving polypharmacy (generally considered as 6 or more medications). Another international study also indicated that multi-comorbidities were higher in the 2-ART cohort compared with 3-ART cohort [21]. The authors also found that patients initiation 2-ART were older, had similar regimens compared to our study, and had shorter time-to-discontinuation. [21] Although we did not test any causality, it seems logical that patients who are older, have more co-morbidities, and take more co-medications will likely need a treatment strategy to reduce drug-drug interaction (DDI) or drug adverse events. A 2-ART can be one option for these patients. Also, the higher proportion of renal disease (34.0% vs. 4.8%; $p < 0.0001$), hemodialysis (6.4% vs. 0.2%; $p < 0.0001$) and bone disorders (18.1% vs. 6.3%; $p < 0.0001$) in the 2-ART cohort compared with 3-ART cohort might be a reason for the choice of NRTI-sparing regimen. Some studies have demonstrated that greater decrease in renal function and bone mineral density (BMD) were observed in subjects treated with TDF-containing regimens than were observed in subjects treated with TDF-sparing regimens. TDF was well known to cause the proximal tubular and renal toxicities especially in patients with small body weight not only in Japanese but also

Vietnamese populations [22–24], and they were irreversible after a certain period of TDF use [25]. NRTI-sparing regimen comprised the majority of all 2-ARTs in our study, which might suggest that TDF-sparing strategies were adopted to avoid these toxicities. Thus, resorting to non-standard regimens based on patients' more complex and sicker profiles reflect the strategy that we refer to as “negative selection”. In contrast, patients who are not as sick as the population identified in our study may be also placed on 2-ART regimens an option, especially for naïve patients or treatment-experienced patients with few complications as these could be switches for convenient purposes. We refer to 2-ART regimen selection of this nature as “positive selection”.

When stratifying by time periods that reflected the commercial availability of specific antiretrovirals in Japan, there was a shift in drug class among the NRTI-sparing regimens; PI + INSTI regimens were dominant from April 1, 2008 to September 30, 2014, whereas NNRTI + INSTI regimens were dominant from October 1, 2014 to April 30, 2019. With increase in variety of ART treatment options, 2-ART combinations seemed to be personalized to individuals and has become diverse. Accordingly, the shift to NNRTI + INSTI as represented by “dolutegravir + rilpivirine” has increased as a new NRTI-sparing regimen. The most common switching pattern of NRTI-sparing regimen with PI + INSTI to standard 3-ART with INSTI + 2NRTI might have occurred because a randomized study (NEAT001/ANRS143) suggested that “raltegravir + darunavir/ritonavir” group have more failures in patients with low baseline CD4 cell count [26].

Some debate remains about the usefulness to switch from a 3-ART to a 2-ART regimen. Some experts cite pharmacodynamics concerns about drug plasma level variability with a 2-ART [27], while others cite the benefits of a reduced pill burden by switching that could lead to better treatment adherence [28]. In the current study, more patients in the 2-ART than the 3-ART cohort switched their ART regimen with a switch rate that was approximately two times higher. Again, this might imply some challenges in managing patients on 2-ART. Two interpretations of these results can be discussed. Either patients were too complex to be managed on a long-term basis, or the 2-ART were not as efficacious or safe compared to the 3-ART. Our study has clearly characterized patients on 2-ART might be difficult to treat regardless of 2 or 3-ART. Another potential reason for a higher switch-rate and earlier switches might be that the 2-ART was not as efficacious or safe as compared SoC 3-ART. Several studies on 2-ART have demonstrated heterogeneous results [29–31], some demonstrating inferiority compared to SoC. Recently several 2-ARTs have demonstrated non-inferiority and are now approved in several countries. Since these studies were usually done in the optimal settings of randomized controlled trials with a very controlled patient population, data from real-world settings will need to demonstrate the robustness of these regimens. The reasons for drug switching were not recorded in the MDV database; however, potential reasons include drug-drug interaction, drug resistance or adherence issues. As PLWH in Japan have been noted to have good drug adherence [15], the reasons could be related to negative selection and the unique comorbidities and co-medications of this population.

There are several limitations inherent in database studies that should be noted. The MDV database is not representative of all PLWH in general because hospitals with advanced medical care capabilities are

included in the database. Doctors' choices of ART regimens or switching strategies may also differ not only among hospitals in the database but also between these hospitals and HIV-specialized facilities. There may be misclassification of 2-ART and 3-ART cohort due to the assumption that all components of the regimen are prescribed on the same day. It is also not possible to track patients as they move between hospitals. To address this shortfall, sensitivity analysis was performed that required patients to meet criteria for inclusion as "continuously" receiving care and assessed patients from their first captured switch in the database. There may still be differential follow-up time between 2-ART and 3-ART cohort beyond one year, a potential remaining source of bias when evaluating switch rates. Limitations also exist with the switch analysis for the 3-ART cohort as, due to limited sample size, any patient on a 2-antiretrovirals was classified into the 2-ART cohort. Therefore, a 3-ART switch could not drop to a 2-ART. In addition, with the 2-ART cohort, the index date is date of initiation of the 2-ART, which could be quite far along in their treatment history and likely when they are older. Finally, lab results, such as viral load and CD4 + counts, were not recorded in the database, only the number of the test was recorded. Therefore, the clinical effects of 2- versus 3-ART could not be assessed.

This study was the first step in understanding patient profiles and medical needs of those who benefit from 2-ART in Japan. It provides a foundation for future studies to further analyze and explore reasons for switching, as well as identifying those may most benefit from NRTI-sparing regimen. As it is expected that more patients will receive 2-ART by positive selection in the future, research characterizing the benefits of these regimens is imperative.

Conclusion

In conclusion, patients on 2-ART demonstrated to have complex profiles, are older, and have more comorbidities and co-medications compared to patients on 3-ART. This highlights the negative selection of 2-ART regimens and the need for careful management by physicians to reduce treatment-related toxicities up to now.

Abbreviations

2-ART
2-drug ART
3-ART
3-drug ART regimen
AE
Adverse event
ART
Antiretroviral therapy
BMD
Bone mineral density
CCI

Charlson Comorbidity Index
CCR5
Chemokine receptor type 5
ICD-10
International Classification of Diseases, 10th Revision
INSTI
Integrase strand transfer inhibitors
MDV
Medical Data Vision
NRTI
Nucleoside reverse transcriptase inhibitor
NNRTI
Non-nucleoside reverse transcriptase inhibitor
PI
Protease inhibitor
PLWH
People living with HIV
SOC
Standard of care
TDF
Tenoovir disoproxil fumarate
TAF
Tenofovir alafenamide
WHO
World Health Organization
UNAIDS
United Nations Programme on HIV/AIDS

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Rinsyou Kenkyuu Suishin Network Japan Ethics Committee (Approval Number: 518-NIS-8422). The Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (<http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000153339.pdf>) do not apply to studies exclusively using de-identified data, we were not obligated to obtain informed consent in this study.

Consent for publication

Not applicable.

Availability of data and materials

This study used a commercial database provider, Medical Data Vision, Co., Ltd. (MDV), to source a de-identified dataset. Sharing MDV data is difficult because of the contractual agreements between MDV and medical facilities. For inquiries about access to the dataset used in this study, please contact MDV (website, <https://www.mdv.co.jp/>; e-mail, ebm_sales@mdv.co.jp).

Competing interests

The authors have no competing interests to declare.

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Authors contributions

DJR, NK, MK, MY contributed to the conception of the study and all authors contributed to the design of the study. NO, MK, JY contributed to the data analysis, and DJR, NK, BC, KT and SO contributed to the data interpretation. NK, MK and JY were involved in drafting the manuscript, and DJR, BC, KT and SO revised it critically. All authors read and approved the final manuscript.

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Figures

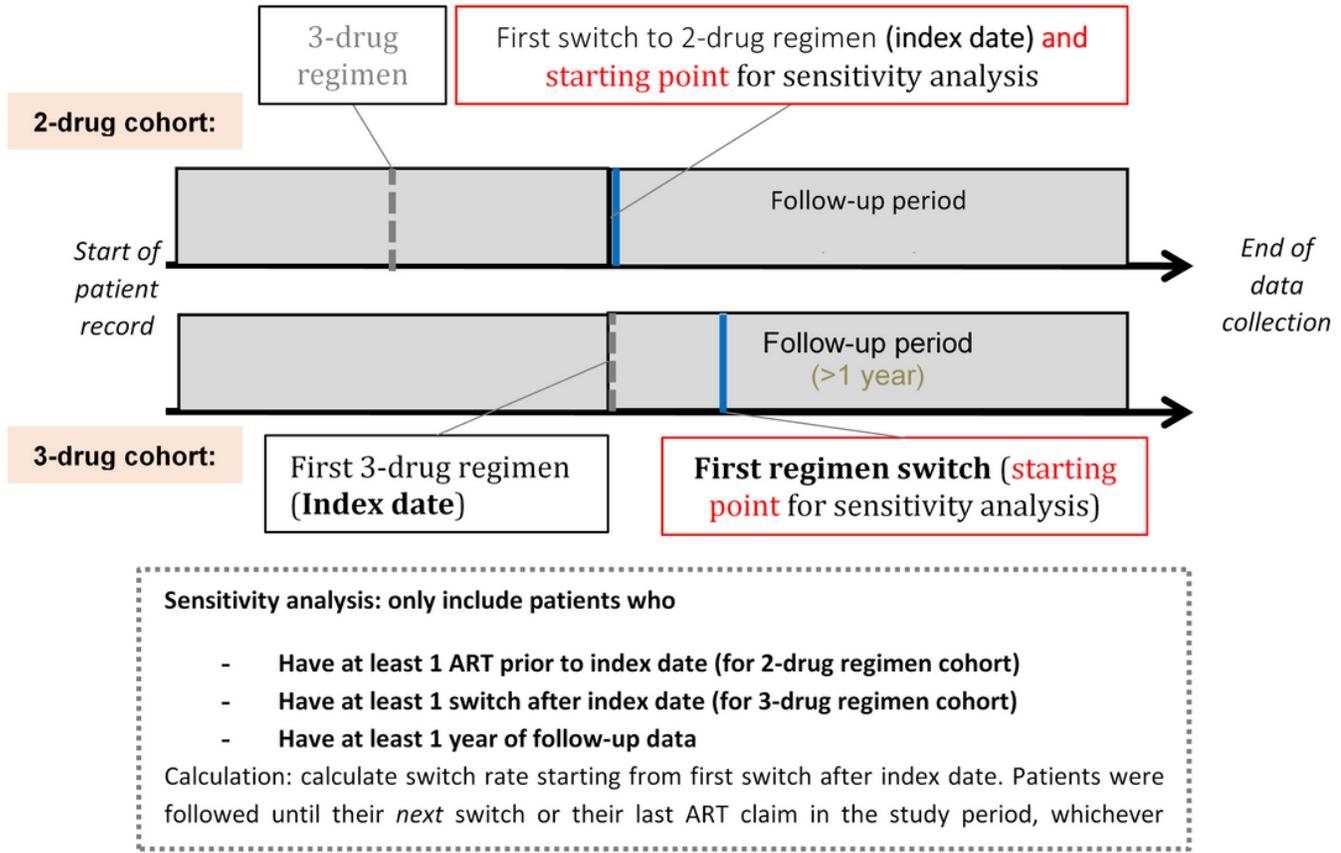


Figure 1

Sensitivity analysis for the exploratory objective

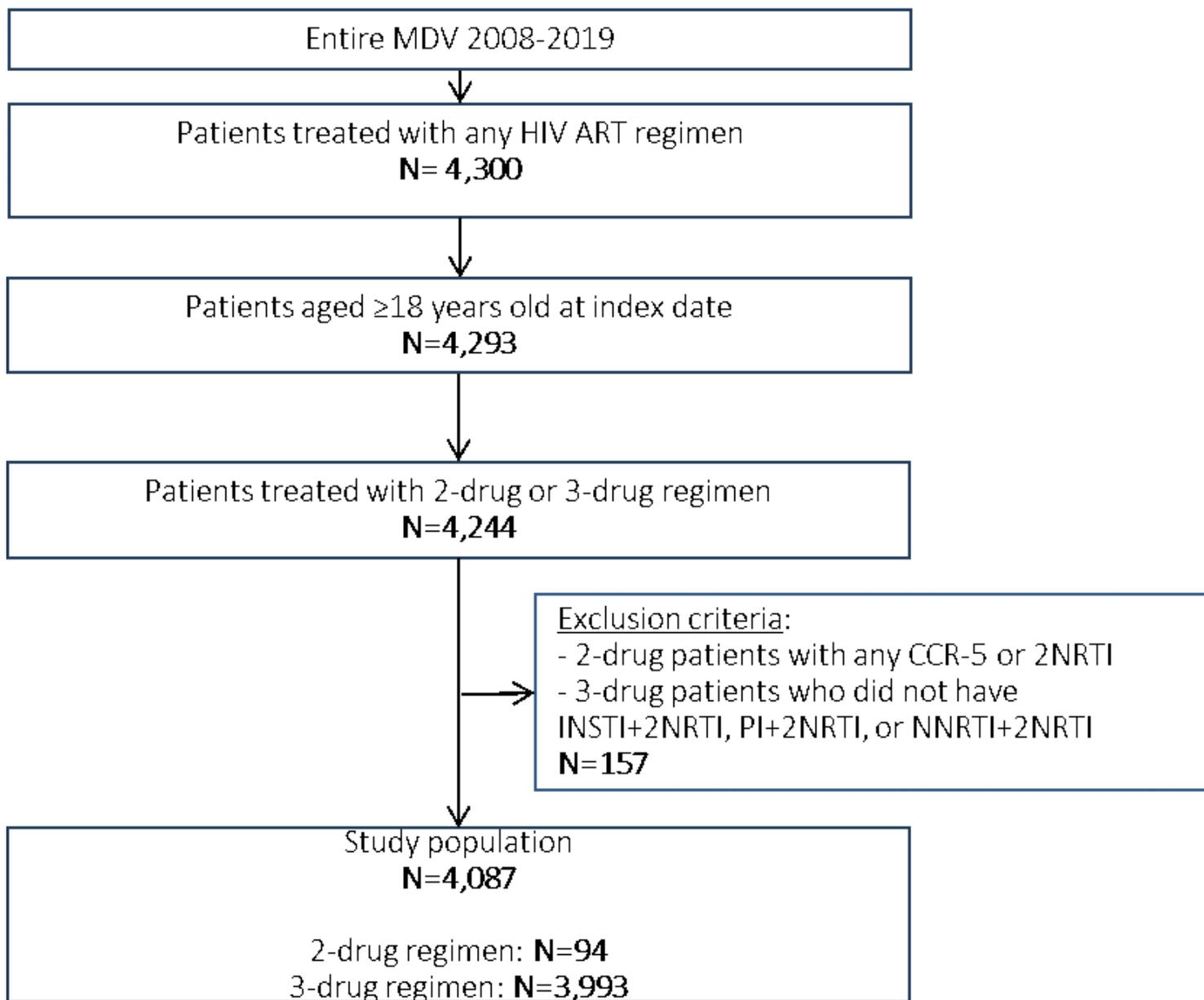


Figure 2

Flow chart of patient attrition

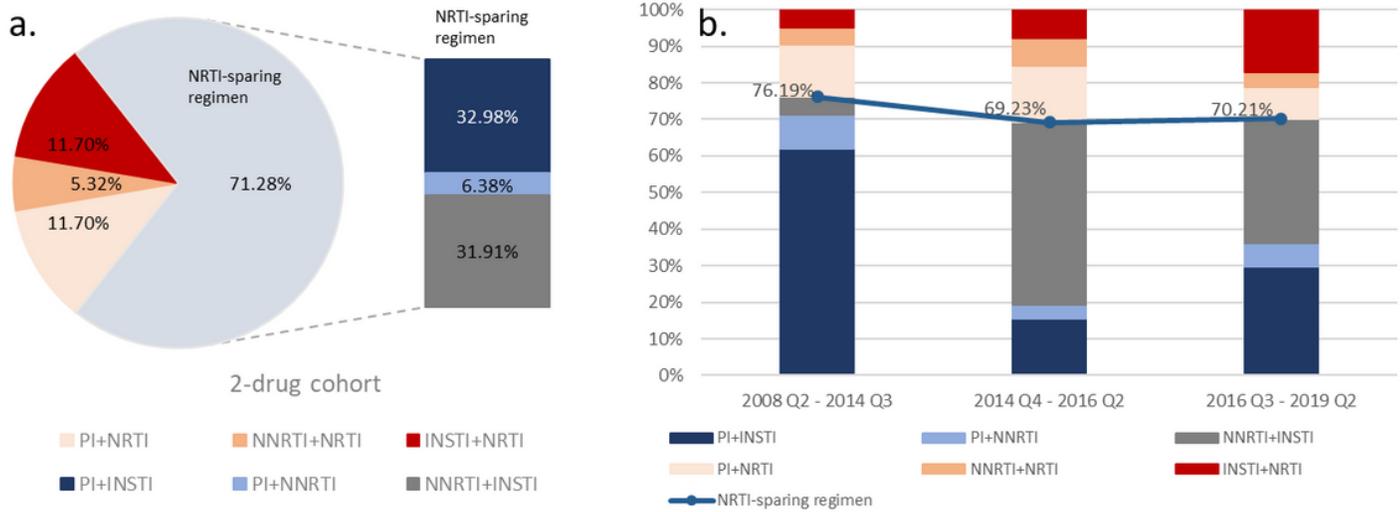


Figure 3

Analysis of drug regimens. (a) Treatment patterns by drug combination regimen at index date. (b) Drug combinations over three periods for the 2-drug cohort.

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