Original Article

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Characteristics of adverse event reports among people living with human immunodeficiency virus (HIV) in Japan: Data mining of the Japanese Adverse Drug Event Report database

Hiroyuki Tanaka[1,*], Mitsutoshi Satoh[2], Masaki Takigawa[1,3], Toshihisa Onoda[1], Toshihiro Ishii[1]

[1] Department of Practical Pharmacy, Faculty of Pharmaceutical Sciences, Toho University, Chiba, Japan;
[2] Department of Toxicology and Pharmacology, Division of Pharmacy Practice, Meiji Pharmaceutical University, Tokyo, Japan;
[3] Department of Pharmacy, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan.

SUMMARY The development of new anti-HIV drugs and advances in antiretroviral therapy (ART) regimens have enabled longer and more effective treatments in people living with HIV (PLWH). However, the aging of PLWHs is another issue that needs to be addressed. In addition to ART, many PLWHs frequently receive medications for various comorbidities. However, real-world data on the occurrence of adverse events in PLWHs and their causative drugs are rare. Therefore, this study aimed to clarify the characteristics of adverse event reports among PLWHs in Japan. PLWH cases with adverse events were comprehensively searched and analyzed using the Japanese Adverse Drug Event Report database (JADER). Despite changes in guideline-recommended ART regimens, anti-HIV drugs were the main cause of adverse events in PLWHs throughout the study period. However, considerable variations have been observed in the reporting rate of anti-HIV drug classes registered as causative drugs in JADER, especially for anchor drugs. In other words, the reporting rate of integrase strand transfer inhibitors has increased in recent years, while that of protease inhibitors and non-nucleoside reverse transcriptase inhibitors has decreased. Immune reconstitution inflammatory syndrome was the most reported adverse event and was frequently noticed by healthcare providers managing patients with HIV infections. The trends in adverse event reports for female and older patients differed from those for the overall population. This study may provide insights that can help in the establishment of optimal management strategies for PLWHs.

Keywords People living with HIV, adverse events, anti-HIV drug, Japanese Adverse Drug Event Report database

1. Introduction

Current World Health Organization and most national guidelines recommend the initiation of antiretroviral therapy (ART) for all people living with human immunodeficiency virus (HIV) (PLWH) regardless of clinical or immune status (*1-3*). In Japan, combination antiretroviral therapy (cART) with three or more anti-HIV drugs has become available since 1997, and this has inhibited viral proliferation and restored immunity in PLWH (*4*). However, early ART regimens have many clinical limitations, such as various adverse events, interactions with concomitant drugs and food, and a high pill burden (*5*). The development of antiviral drugs, especially anti-HIV drugs, has been a remarkable feat (*6*). Furthermore, anti-HIV drugs developed in recent years have fewer problems than those developed earlier (*5*). Five classes of anti-HIV drugs, classified based on their mechanism of action, are used in Japan: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and C-C chemokine receptor type 5 antagonist (CCR5A) (*3*). HIV treatment guidelines generally recommend ART regimens that consist of two NRTIs as backbone drugs plus a third "anchor drug" from another drug class (INSTI, PI, or NNRTI) (*1-3*). However, with the advent of drugs with high anti-HIV activity in recent years, dual therapy regimens have become an option for eligible patients (*7*). All in all, the treatment modalities for HIV infection are frequently updated, and developing novel anti-HIV drugs and ART regimens has led to decreased HIV-related morbidity and mortality in PLWHs (*8*). However, HIV infection

is a chronic disease that cannot be cured by ART and thus needs lifelong treatment. In addition, an increasing lifetime risk of developing non-AIDS comorbidities owing to the increasing life expectancy and long-term use of ART among PLWHs has become a critical issue (*9-12*).

PLWHs are frequently prescribed drugs to prevent or treat opportunistic infections before or after cART initiation. In addition, with the increased life expectancy of PLWHs, new problems, such as the need for drug therapy for chronic complications associated with the aging of PLWH, have emerged (*9-12*). The proportion of older PLWHs (aged ≥ 50 years) with at least one chronic disease in addition to HIV exceeded 50% in a French study (*9*) and even reached 94% in a United States study (*10*). Regarding comorbidities among PLWHs in Japan, Naito *et al*. analyzed data from the National Database between 2009 and 2019 and found that 81.5% of the patients had chronic comorbidities (*11*). The most frequent comorbidities were diabetes, lipid disorders, psychiatric disorders, and hypertension. Therefore, the management of chronic diseases in PLWHs is becoming increasingly important. In addition, a previous study found that non-AIDS-defining cancers occurred more frequently in PLWHs aged ≥ 60 years, and this was attributed to an increase in older PLWHs (*13*). Therefore, cancer chemotherapy in PLWHs has also become an important consideration in the management of HIV infections.

Thus, PLWHs may frequently receive medications for various comorbidities in addition to ART. However, real-world data on the occurrence of adverse events in PLWHs and their causative drugs are rare. Therefore, this study aimed to comprehensively investigate and characterize the adverse event reports of PLWHs using the Japanese Adverse Drug Event Report database (JADER).

2. Materials and Methods

2.1. Data source

JADER is a large Japanese database that can be used to identify trends in the occurrence of adverse events; it is a spontaneously reporting database made publicly available by the Pharmaceuticals and Medical Devices Agency (*https://www.pmda.go.jp*). In this study, we downloaded and analyzed data registered in JADER in the period between April 2004 and March 2020. The database consists of four file types: "Demo" (patients' demographic information, such as sex and age), "Drug" (*e.g.*, drug name [generic and product names], causal relationship), "Reac" (*e.g.*, adverse events, clinical outcomes), and "Hist" (*e.g.*, medical history, primary disease). Based on their level of involvement in adverse events, drugs in the "Drug" file were assigned to one of three categories: "suspected drug," "interaction," and "concomitant drug."

2.2. PLWH cases

Cases that included anti-HIV drugs (Table S1, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=148*) in the "Drug" file and/or those that included terms related to HIV infection (Table S2, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=148*) in their "Hist" file were selected as PLWH cases. Given that lamivudine, tenofovir disoproxil fumarate, and tenofovir arafenamide fumarate are also used to treat hepatitis B virus infection, cases judged to have been treated for diseases other than HIV infection or unknown based on the product name, dose, and medical history were excluded from the analysis. In addition, cases treated with zidovudine in combination with interferon alpha for low-grade adult T-cell leukemia lymphoma were also excluded. Moreover, cases treated with lopinavir/ritonavir combination, an anti-HIV drug that was used for COVID-19 treatment, were excluded.

2.3. Causative drugs

Drugs registered as "suspected drug" or "interaction" in JADER were redefined as "causative drug" of adverse events, and all causative drugs reported in PLWHs were counted. The main ingredients of fixed-dose combinations of anti-HIV drugs were also evaluated. In addition, anti-HIV drugs were classified into five classes (NRTI, NNRTI, PI, INSTI, and CCR5A/fusion inhibitor [FI]) based on their mechanism of action. Given that some anti-HIV drugs belong to same class, drug classes appearing more than once in the same report were counted only once.

2.4. Adverse events

Adverse events were analyzed using the preferred term (PT) and system organ class (SOC) in the Medical Dictionary for Regulatory Activities (MedDRA). In general, adverse events in JADER are based on PTs. As the top level of the MedDRA hierarchy, the SOC provides the broadest concepts for data retrieval. There are a total of 27 SOCs in MedDRA, and the analysis of adverse events coded by PT assigned to the SOC may better reflect the impact on an organ or system of the human body. In this study, all individual PTs were mapped to SOC based on MedDRA. Considering that some PTs may belong to more than one SOC, we counted all SOCs for each. Although different PTs were assigned to the same SOC within the same report after mapping, the duplicated SOC was only counted once.

2.5. Statistical analysis

Demographic characteristics, causative drugs, and

adverse events were summarized descriptively based on the number of cases and their rates. All statistical analyses were performed using Microsoft® Excel® 2016 (Microsoft Corp, Redmond, WA, USA).

3. Results

3.1. PLWH characteristics

Among the 640,991 cases registered in JADER during the study period, 3,337 cases were included in the analysis. Table 1 shows the background data for the 3,337 PLWH cases with adverse events. Males accounted for 87.23%, and those in their 30s-40s accounted for 47.56% of the total population. Figure 1A shows the changes in the number of adverse event reports in PLWH over time. The highest number of reports was in fiscal year (FY) 2004, and the lowest was in FY 2011. The number of adverse event reports in PLWH showed a decreasing trend from FY 2004 to FY 2011. However, it had recently increased to the same level as that of FY 2004. Figures 1B and 1C show the longitudinal changes in the composition rate of sex and age in PLWH with adverse events, respectively. There were no considerable changes in the sex composition rate throughout the study period, whereas the composition of the 20-49 years age group declined in recent years. However, the interpretation of the results should consider the recent increase in the number of reports with incomplete data on sex and age.

3.2. Causative drugs

The causative drugs of some adverse events in more than 30 PLWHs are listed in Table 2. A total of 42 drugs were listed, of which 24 (57.1%) were anti-HIV drugs. Lamivudine was the most frequently reported causative drug, followed by ritonavir, tenofovir disoproxil fumarate, emtricitabine, and abacavir sulfate. When grouped into classes based on their mechanism of action, the reporting rate was higher for NRTIs (71.59%, 2389/3,337 cases), PIs (41.32%, 1379/3,337 cases), INSTIs (26.16%, 873/3,337 cases), NNRTIs (19.60%, 654/3,337 cases), and CCR5A/FI (1.68%, 56/3,337 cases). Furthermore, Figure 2 shows the time trends. In FY 2004, the reporting rate of NRTI, the backbone drag, was 88.05% (280/318 cases), but it has declined to approximately 60-70% since FY 2014. For anchor drugs, the reporting rate of INSTIs had increased in recent years, whereas that of PIs and NNRTIs had decreased.

For non-anti-HIV drugs, the sulfamethoxazole/trimethoprim combination, valganciclovir hydrochloride, doxorubicin hydrochloride, azithromycin hydrate, and atovaquone ranked high among causative drugs (Table 2). The reporting rates for drugs other than anti-HIV drugs

Table 1. Population characteristics

Characteristic	*n* (%)
Total	3337
Sex	
Male	2911 (87.23)
Female	329 (9.86)
Unknown	97 (2.91)
Age (years)	
<10	37 (1.11)
10-19	7 (0.21)
20-29	279 (8.36)
30-39	791 (23.70)
40-49	796 (23.85)
50-59	539 (16.15)
60-69	386 (11.57)
70-79	124 (3.72)
80-89	19 (0.57)
90-99	1 (0.03)
Unknown	358 (10.73)

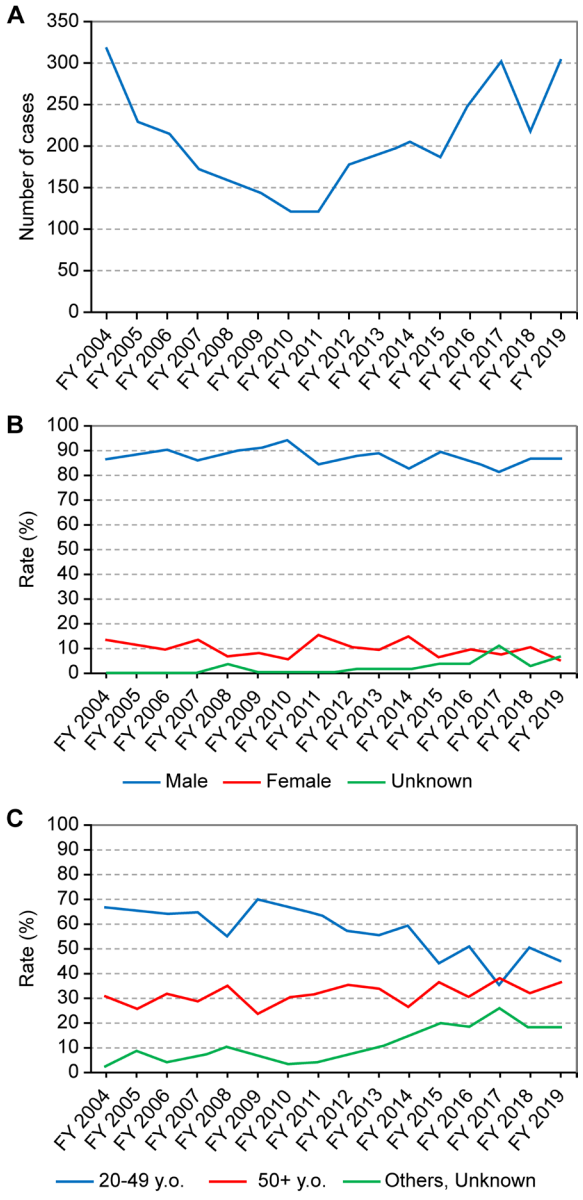

Figure 1. Time trends in the number of PLWH cases with reported adverse events and their sex and age structure. **(A)** Number of PLWH cases. **(B)** Composition rate of sex. **(C)** Composition rate of age groups

Table 2. Causative drugs of adverse events in more than 30 PLWH cases

Causative drugs	Reporting rate (*n*, %)
Lamivudine	1311 (39.29)
Ritonavir	1058 (31.71)
Tenofovir disoproxil fumarate	951 (28.50)
Emtricitabine	843 (25.26)
Abacavir sulfate	786 (23.55)
Efavirenz	498 (14.92)
Dolutegravir sodium	472 (14.14)
Lopinavir	455 (13.64)
Zidovudine	428 (12.83)
Sanilvudine	410 (12.29)
Raltegravir potassium	372 (11.15)
Darunavir ethanolate	358 (10.73)
Atazanavir sulfate	339 (10.16)
Tenofovir arafenamide fumarate	185 (5.54)
Sulfamethoxazole/Trimethoprim combination	178 (5.33)
Nelfinavir mesylate	153 (4.58)
Didanosine	132 (3.96)
Valganciclovir hydrochloride	122 (3.66)
Fosamprenavir calcium hydrate	110 (3.30)
Doxorubicin hydrochloride	85 (2.55)
Cobicistat	83 (2.49)
Azithromycin hydrate	81 (2.43)
Atovaquone	69 (2.07)
Prednisolone	66 (1.98)
Ethambutol hydrochloride	65 (1.95)
Rilpivirine hydrochloride	63 (1.89)
Elvitegravir	62 (1.86)
Nevirapine	60 (1.80)
Ribavirin	55 (1.65)
Indinavir sulfate ethanolate	55 (1.65)
Ganciclovir	54 (1.62)
Maraviroc	53 (1.59)
Clarithromycin	52 (1.56)
Rifabutin	46 (1.38)
Etravirine	46 (1.38)
Fluconazole	44 (1.32)
Peginterferon alfa-2b (Genetical Recombination)	43 (1.29)
Vincristine sulfate	43 (1.29)
Cyclophosphamide hydrate	39 (1.17)
Amphotericin B	33 (0.99)
Foscarnet sodium hydrate	30 (0.90)
Pentamidine isetionate	30 (0.90)

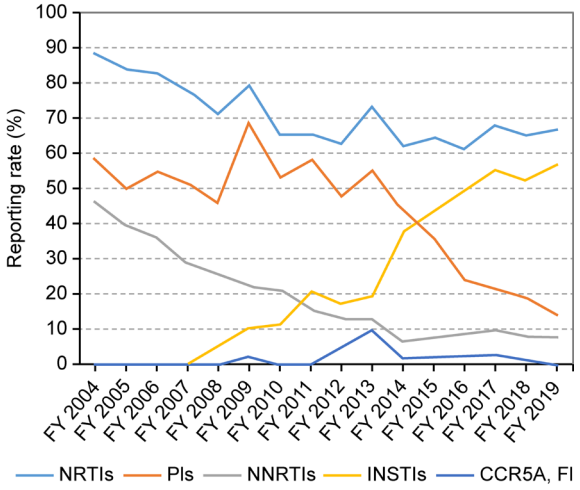

Figure 2. Time trends in reporting rates of anti-HIV drug-related adverse events by drug mechanism of action. NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; CCR5A, C-C chemokine receptor type 5 antagonist; FI, fusion inhibitor

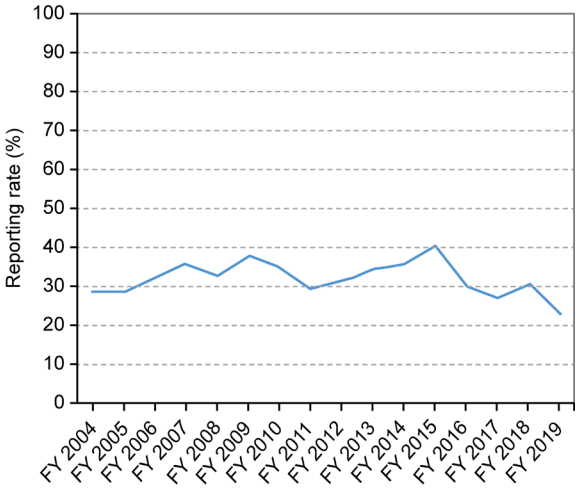

Figure 3. Time trends in reporting rates of non-anti-HIV drug-related adverse events.

ranged from 22.9% to 39.9% throughout the study period (Figure 3).

3.3. Adverse events

Table 3 summarizes the top 20 adverse events reported at the PT level. The most frequently reported adverse event was immune reconstitution inflammatory syndrome (IRIS) (346/3,337 cases, 10.37%), followed by renal impairment (178/3,337 cases, 5.33%), anaemia (122/3,337 cases, 3.66%), diabetes mellitus (99/3,337 cases, 2.97%), and hepatic function abnormal (88/3,337 cases, 2.64%). Table 4 summarizes the reported adverse events at the SOC level. "General disorders and administration site conditions" (649/3,337 cases, 19.45%) was the most frequently reported, followed by "immune system disorders" (625/3,337 cases, 18.73%), "infections and infestations" (605/3,337 cases, 18.13%), "metabolism and nutrition disorders" (552/3,337 cases, 16.54%), and "blood and lymphatic system disorders" (500/3,337 cases, 14.98%). The SOC-level adverse events according to sex and age are shown in Figure 4. The trends for females and those aged ≥ 50 years were different from those in the overall population. Among females, "immune system disorders" (68/329 cases, 20.67%) and "metabolism and nutrition disorders" (68/329 cases, 20.67%) were the most commonly reported, followed by "blood and lymphatic system disorders" (66/329 cases, 20.61%), "general disorders and administration site conditions" (51/329 cases, 15.50%), and "infections and infestations" (51/329 cases, 15.50%). In addition, "reproductive system and breast disorders" and "gestational and perinatal conditions" were mostly reported in females, probably because

Table 3. Top 20 adverse events at the PT level

PT	Reporting rate (*n*, %)
Immune reconstitution inflammatory syndrome	346 (10.37)
Renal impairment	178 (5.33)
Anaemia	122 (3.66)
Diabetes mellitus	99 (2.97)
Hepatic function abnormal	88 (2.64)
White blood cell count decreased	77 (2.31)
Liver disorder	70 (2.10)
Rash	65 (1.95)
Pyrexia	65 (1.95)
Acute kidney injury	63 (1.89)
Cytomegalovirus chorioretinitis	59 (1.77)
Pancytopenia	57 (1.71)
Platelet count decreased	56 (1.68)
Diarrhoea	54 (1.62)
Pneumocystis jirovecii pneumonia	47 (1.41)
Drug eruption	45 (1.35)
Nausea	45 (1.35)
Renal disorder	44 (1.32)
Vomiting	42 (1.26)
Myelosuppression	41 (1.23)

Table 4. Adverse events at the SOC level

SOC	Reporting rate (*n*, %)
General disorders and administration site conditions	649 (19.45)
Immune system disorders	625 (18.73)
Infections and infestations	605 (18.13)
Metabolism and nutrition disorders	552 (16.54)
Blood and lymphatic system disorders	500 (14.98)
Vascular disorders	451 (13.52)
Nervous system disorders	450 (13.49)
Renal and urinary disorders	444 (13.31)
Investigations	431 (12.92)
Hepatobiliary disorders	405 (12.14)
Gastrointestinal disorders	382 (11.45)
Skin and subcutaneous tissue disorders	352 (10.55)
Respiratory, thoracic and mediastinal disorders	269 (8.06)
Cardiac disorders	236 (7.07)
Endocrine disorders	231 (6.92)
Musculoskeletal and connective tissue disorders	212 (6.35)
Injury, poisoning and procedural complications	207 (6.20)
Psychiatric disorders	186 (5.57)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	186 (5.57)
Eye disorders	122 (3.66)
Pregnancy, puerperium and perinatal conditions	63 (1.89)
Congenital, familial and genetic disorders	32 (0.96)
Reproductive system and breast disorders	31 (0.93)
Surgical and medical procedures	20 (0.60)
Ear and labyrinth disorders	13 (0.39)
Social circumstances	2 (0.06)
Product issues	1 (0.03)

of biological differences. In those aged ≥ 50 years, "metabolism and nutrition disorders" (202/1,069 cases, 18.90%) were the most commonly reported, followed by "renal and urinary disorders" (188/1,069 cases, 17.59%), "infections and infestations" (166/1,069 cases, 15.53%), "vascular disorders" (164/1,069 cases, 15.34%), and "nervous system disorders" (160/1,069 cases, 14.97%).

4. Discussion

The actual status of adverse event reports in PLWH remains unclear. In this study, anti-HIV drugs were the main causative drugs for adverse events in PLWHs throughout the study period. However, age composition and causative drugs also changed markedly during the study period. In addition, by analyzing the PT and SOC levels in the MedDRA hierarchy, it was possible to characterize the adverse events reported in PLWH cases. To our knowledge, this is the first study to identify trends in adverse event reports in PLWH in the real world using the JADER. Our study identifying the characteristics of adverse event reports among PLWHs in Japan has important implications for establishing optimal management strategies for this population.

Males accounted for 87.23% of the cases, consistent with findings that males account for more than 90% of PLWHs receiving cART in Japan (*14*). The annual number of reports differed to up to 196. Overall, the number of reports decreased until FY 2011 and then increased thereafter. This change in the number of reports may be related to the status of the development of an infrastructure for pharmacovigilance in Japan (*15*). It may also reflect adverse events associated with the long-term use of anti-HIV drugs and/or the "Weber effect" (*16*) on new drugs. In any case, future trends in the number of reports should be monitored. The time trends of the age structure of PLWHs with adverse events may reflect the aging of PLWHs in Japan. However, it should be noted that, in recent years, an increasing number of reports have provided unclear information on age. Nevertheless, it appears that the reporting rate for the 20-49 years age group has decreased, while that for the ≥ 50 years age group has increased.

A total of 42 drugs, 24 of which were anti-HIV drugs, were reported as causative drugs in more than 30 PLWHs. The top five causative drugs were lamivudine, ritonavir, tenofovir disoproxil fumarate, emtricitabine, and abacavir sulfate. Of these, lamivudine, tenofovir disoproxil fumarate, emtricitabine, and abacavir sulfate are NRTIs and are included in most standard ART regimens. Ritonavir inhibits intestinal and hepatic cytochrome P450 3A, and low-dose ritonavir is widely used as a booster for other PIs. This could explain these drugs being the top causative drugs of adverse events. The other causative drugs were efavirenz, an NNRTI; dolutegravir sodium, an INSTI; and lopinavir, a PI. Their reporting rates were similar (14.92%, 14.14%, and 13.64%, respectively). With respect to anti-HIV drug class, it varied markedly throughout the study period, which may have been influenced by the guideline recommendation of cART (*1-3*). In contrast, non-anti-HIV drugs accounted for only approximately 20-40% of adverse events cases throughout the study period.

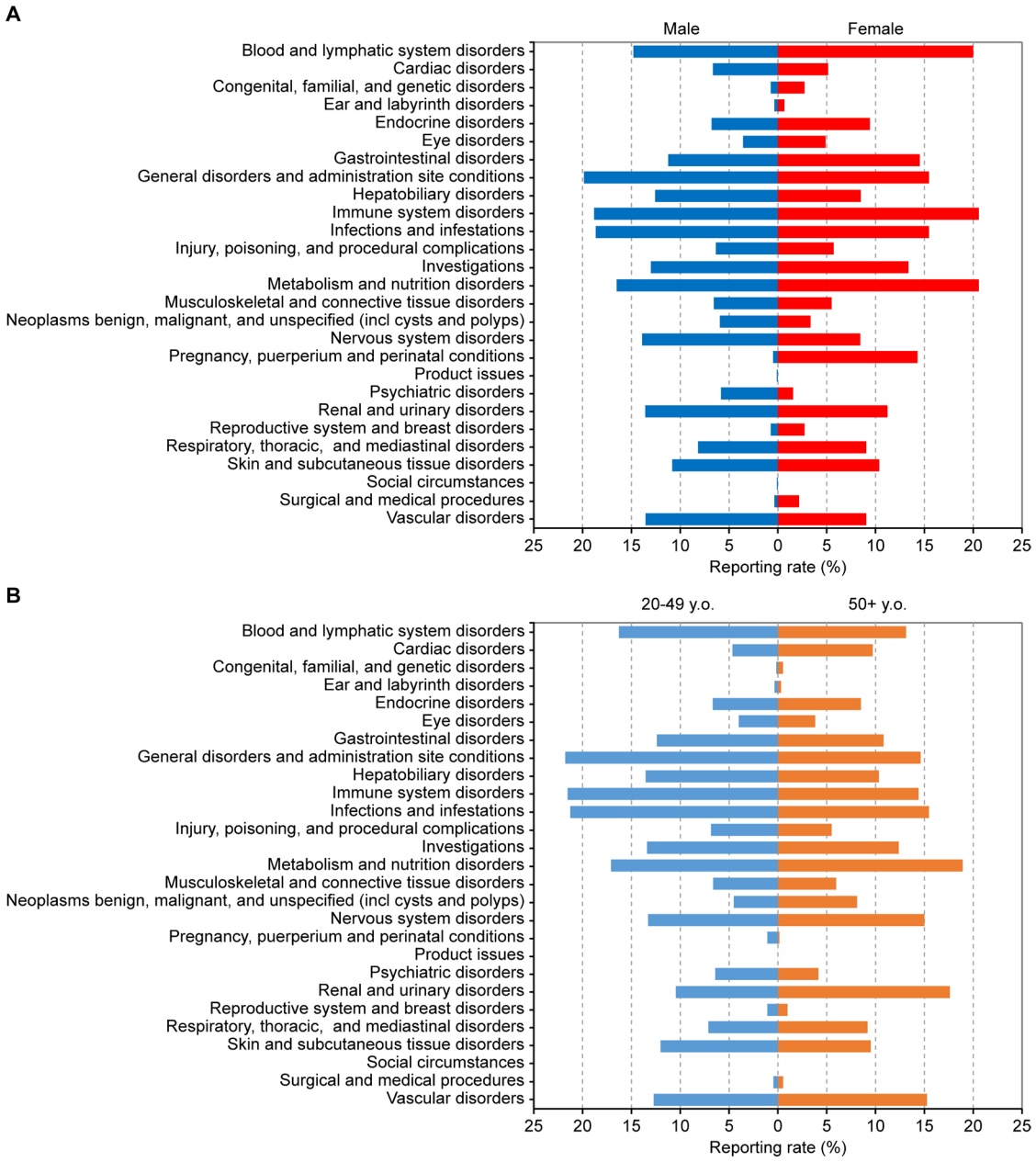

Figure 4. Comparison of adverse events at the SOC level by sex and age group. (A) Reporting rates by sex. **(B)** Reporting rates by age group.

Apparently, anti-HIV drugs were the primary causative drugs of adverse events in PLWHs. The most common non-anti-HIV drugs that caused adverse events were those used to prevent or treat AIDS-related diseases (opportunistic infections and AIDS-related cancers). Therefore, even if HIV infection can be controlled by cART, adverse events associated with these drugs must be carefully monitored. Using a large Japanese healthcare database, Ruzica *et al*. analyzed the 10 most common co-medications in PLWHs treated with cART. They found that all top 10 medications had higher rates of use in PLWHs than in the non-HIV-infected population (*17*). Therefore, healthcare providers involved in the treatment of HIV infection should also pay attention to the occurrence of adverse events associated with the use of these drugs.

In this study, IRIS was the most frequently reported adverse event at the PT level. IRIS is an undesirable disease- or pathogen-specific inflammatory reaction that may be triggered by the restoration of immune system function following cART initiation (*18*) and is a characteristic adverse event among PLWHs. This result is expected to some extent in studies of PLWH cases that use spontaneous reporting of adverse event databases, such as the current study. Common or high-incidence adverse events are not necessarily reported more frequently. The disadvantage of studies using spontaneous reporting adverse event databases is that it is not possible to calculate the incidence of adverse events owing to the lack of a denominator (*19*). However, if

the study is limited to a particular population, it may be possible to identify adverse events and the risk factors that are characteristic of that population. We focused on this feature and reported the results of our analysis of factors affecting the clinical outcomes of IRIS using the JADER (*20*). It may also be better to conduct an analysis at the SOC level rather than at the PT level to characterize adverse events occurring in a particular patient population. For example, "hepatic function abnormal" and "liver disorder" at the PT level (Table 2) may not be clinically distinct. These two PTs are classified as "hepatobiliary disorders" at the SOC level. The analysis of adverse events at the SOC level can better reflect their effects on human organs and systems. The top five SOC-level adverse events in this study were general disorders and administration site conditions, immune system disorders, infections and infestations, metabolism and nutrition disorders, and blood and lymphatic system disorders. However, it has been suggested that the occurrence of adverse events is influenced by sex and age, including in PLWHs (*21*). Thus, because 87.23% of the study population was male, the above results strongly reflect the status of adverse event reports in males. Therefore, when we analyzed SOC-level adverse events by sex and age, we found that the trends in females and in those aged ≥50 years were different from that in the overall group.

Recently, the life expectancy of properly treated PLWHs has approached that of non-HIV-infected individuals owing to the excellent efficacy of cART (*8*). However, the increasing number of PLWHs with comorbidities and the adverse events associated with long-term exposure to anti-HIV drugs have become a problem with the aging of PLWHs (*9-12*). Medications for comorbidities can cause problems related to polypharmacy and drug interactions (*22*). This problem is further complicated by an aging-related physiological decline (*23*).

Our study has some limitations. First, data from spontaneous reporting adverse event databases, such as JADER, has issues of over-reporting, under-reporting, missing data, lack of a denominator, and the presence of confounding factors (*19*). Second, adverse events are not always induced by treatment. Particularly, PLWHs are known to have higher rates of cardiovascular, renal, neurocognitive, oncology, and osteoporotic diseases than non-HIV-infected individuals (*12*). These factors may have affected the current analysis. Third, although trends in adverse event reports among PLWHs were examined in this study, the influence of the drug on the occurrence of each adverse event was not assessed.

In conclusion, despite the improved efficacy and safety of cART, anti-HIV drugs remain the leading cause of adverse events in PLWHs. In addition, the trends in adverse events differed according to sex and age, with females and those aged ≥ 50 years showing trends different from that in the overall population. Thus, the management of HIV infection and drug-related adverse events should consider age and sex. The findings of this study will be helpful for establishing optimal management strategies for PLWHs.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Address correspondence to:
Hiroyuki Tanaka, Department of Practical Pharmacy, Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan.
E-mail: hiroyuki.tanaka@phar.toho-u.ac.jp

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