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Advances in HIV management and challenges in Japan: Current situation of pre-exposure prophylaxis in Tokyo

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Abstract: Since the world's first case series of human immunodeficiency virus (HIV) infection were reported, more than 40 decades have passed. The advancement of HIV treatment and prevention has progressed drastically. Especially, the efficacy of pre-exposure prophylaxis (PrEP) for HIV prevention has been proven by a number of trials and the number of new HIV cases has declined over the years due to the large-scale and rapid implementation of PrEP and universal HIV treatment in multiple countries. However, in Japan, PrEP is not approved or officially supported as of June 2024. Despite of the absence of top-down movement, men who have sex with men (MSM)-friendly private clinics initiated prescriptions of generic medicines for oral PrEP with necessary tests in Tokyo, which greatly contributed to improve access to PrEP. It is of note that current situation of bottom-up PrEP implementation using generic medicines in Tokyo is obviously cost-saving, which is needless to evaluate. However, expense of PrEP is fully out-of-pocket, which will hinder those with low or no income from accessing PrEP services despite the low prices of generic medicines. Furthermore, current PrEP implementation based on user-friendly clinics is functioning only in Tokyo. The role of public health authorities is important to solve these financial and geographical disparities in accessing PrEP services, without impairing existing virtues of accessibility and cost-saving in the current system.

***Keywords*:** HIV, antiretroviral therapy, preexposure prophylaxis

Introduction

Since the world's first case series of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) reported in the United States in 1981 (*1-3*), more than 40 decades have passed. The advancement of HIV treatment and prevention has progressed drastically. Regarding the treatment, combination antiretroviral therapy (cART) became available in 1996 (*4-5*) and has been improving the prognosis of people living with HIV (PLWH) (*6,7*). In addition, the Strategic Timing of Anti-Retroviral Treatment (START) study illuminated that outcomes were better in PLWH who initiated immediate ART (CD4 counts > 500/mm^3) compared to PLWH who initiated deferred ART (CD4 counts < 350/mm^3) (*8*). This promoted early initiation of ART even in asymptomatic PLWH, regardless of CD4 counts, and improved their prognosis. Furthermore, integrase inhibitors (INSTI), especially the third generation INSTI such as bictegravir and dolutegravir, contribute to better quality of life with less adverse effects and less drug-drug interactions compared to other classes of antiretroviral agents (*9-13*). Thus, recent trends of ART are heading to long-acting injection drug and two-drug regimens instead of three-drug for further adherence and theoretically less toxicity, respectively (*14-18*). Along with these accomplishments by ART, current issues in PLWH are mainly related to aging and life style. Causes of death have been changing and the number of non-AIDS defining diseases and mental health related deaths exceeded that of AIDS related (*19*).

The advancement of prevention worldwide has also been significant in this decade. HIV prevention trial network (HPTN) study group conducted the HPTN 052 study, demonstrating that early ART initiation prevented more than 96% of genetically linked infections with the index cases in serodiscordant heterosexual couples (*20*). The extension of this study concluded no linked infections in their partners were observed when HIV viral load was suppressed by ART during more than 5 years of observation (*21*). Another study of serodiscordant gay couples (PARTNER study) also reported similar results, supporting the account that HIV transmission becomes zero when HIV viral load is suppressed (*22*). These findings lead to announce campaigns of "the undetectable equals untransmittable (U=U)". U=U is important in terms of not only public health but also alleviation of stigma of HIV. This concept of treatment as prevention (TasP) has been established through evidence

and contributed to prognosis and public health as well.

However, TasP is not the measure of HIV prevention which people themselves at great risk of HIV acquisition can take voluntarily. In this aspect, pre-exposure prophylaxis (PrEP) has been adopted worldwide as an important preventive strategy. The efficacy of PrEP for HIV prevention has been proven by a number of trials and implementations in many countries (*23-26*). Actually, the number of new HIV cases has declined over the years due to the large-scale and rapid implementation of PrEP and universal HIV treatment in multiple countries (*27-33*). In this review, we discuss current situations and challenges in Japan based upon these worldwide advancements in the field of HIV infection.

Epidemiology of HIV infection in Japan

As of December 2022, the accumulated cases of HIV infection in Japan were 34,421, of which 10, 558 (30.7%) were categorized as AIDS at the HIV diagnosis. The diagnosed cases in each year peaked at 1590 cases in 2012 and showed a decreasing trend to 884 cases in 2022 (*34*). The route of HIV infection is mainly men who have sex with men (MSM) which accounts for 64.5% of the total diagnosis in 2022. This could be an underestimate because of hesitancy in disclosing their sexuality. 12.8% were categorized as unknown for the route of HIV infection, which may reflect the stigma of HIV and being a sexual minority. About 95% of the diagnosed cases were men and 81.8%, 14.6%, 2.0% and 2.3% were Japanese men, foreign men, Japanese women and foreign women, respectively. As for geographical distribution, HIV cases per population in Japan (124,946,789) as of October 2022 (Vital Statistics) was 0.71/100,000 in 2022, which is lower compared to Western countries.

Influence of the COVID-19 pandemic on the decrease in HIV diagnosis since 2020 was concerning based on the decrease in the number of HIV tests provided by public test centers in Japan, which was 142,260 in 2019, 68,998, in 2020, 58,172 in 2021 and 73,104 in 2022 (*34*). However, this decreasing trend, also observed in early 2010s, is likely due to the widespread adoption of the "test and treat" strategy. In this respect, the Joint United Nations Program on HIV/AIDS (UNAIDS)'s 90-90-90 HIV testing and treatment cascade targets by 2020 (90% of people living with HIV know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, and 90% of all people receiving antiretroviral therapy will have viral suppression), currently 95-95-95 targets by 2025, has been playing an important role worldwide. These cascade targets aimed for 90 % of all PLWH to be diagnosed of their HIV-positive status, 90% of those diagnosed with HIV to receive ART, and 90% of people receiving ART to suppress their HIV viral load. Regarding the 90-90-90 targets in Japan, Iwamoto *et al.*, estimated these targets as follows: 85.6% (22,840/26,670), 82.8% (18,921/22,840) and 99.1% (18,756/18,921), based on the data on universal donation records (2011-2015), national surveillance data, and nationwide questionnaires (*35*).

The first and second 90 target and challenges in HIV testing and early ART initiation

Related to the first 90, the estimated number of undiagnosed PLWH in Japan was between about 4000 and 5000 across studies performed by different methods (*35-37*). As the COVID-19 pandemic undermined HIV test provision systems all over the world (*38-40*), provision of HIV test needs to be resilient and be more accessible in order to achieve the first 95 target. In this sense, self-testing or home specimen collection testing is recommended by the CDC, WHO, and other institutions in the world (*41,42*). Although self-collection testing has been increasing in number (from 26,000 tests in 2005 to 91,000 tests in 2016) in Japan (*43*), these tests are currently not approved and not yet covered by health insurance. Prompt adoption of these modalities will contribute to accomplishing the first 95 target. In addition to self-sampling testing, the number of out-of-pocket HIV testing offered by private STI clinics without health insurance coverage has been increasing especially in metropolitan areas like Tokyo due to its convenience, accessibility and anonymity, complementing the shortage of HIV testing in public health centers. However, these private clinics are located mainly in Tokyo and geographic disparity exists in terms of provision of HIV testing. The capacity of public health centers are limited especially in non-metropolitan areas and public HIV testing programs may be disproportionally affected in these areas by the COVID-19 pandemic.

According to the national surveillance data of HIV by 47 prefectures, the total diagnosed cases of HIV infection between 2018 and 2022 per 100,000 population in descending order by area was Tokyo (2.06), Fukuoka (1.23), Okinawa (1.23), Osaka (1.03) and Kumamoto (0.93) (*44*). The proportion of the number of AIDS cases in the number of total HIV cases in these areas were 18.2%, 38.2%, 41.5%, 23.2% and 48.0%, respectively. The average percentage in Japan was 29%. The high proportion of AIDS cases are thought to be a reflection of insufficient HIV testing provision, given that PrEP is not officially approved in Japan. To close the gap, investment in public health centers and adoption of self-sampling testing need to be promoted.

The second 90 target was also not achieved in Japan, probably due to restrictions in the timing of ART initiation regulated by the disabled person's coverage system. In Japan, ART is quite accessible for most PLWH, being covered by national health insurance plus the disabled person's coverage system. However, there are cases in which the disabled person's coverage is not applicable for PLWH with CD4 counts below 500/mm^3, due to their low HIV viral load. Furthermore, to

obtain the coverage, there is an average wait of two to three months, since two blood tests, 1 month apart, are required to apply for the system (*45*). Although the extent to which these gaps affect the second 90 target is unknown, they should be closed further for PLWH and the community's benefit.

Current situation of PrEP in Japan: The long delay in implementation

The last 90 target is well achieved and there is no gap between Japan and the world. Recent commonly used INSTI powerfully enhanced the achievement of this target in Japan. The biggest gap resides in the field of PrEP. As mentioned above, PrEP is not approved or officially supported as of June 2024. According to previous cohort studies, the incidence of HIV infection among MSM in Tokyo was estimated to be between 3.4 and 3.8 /100 person-years (*46,47*). Prevalence of HIV infection among MSM in Tokyo was reported to be as high as 2.6 to 3.0% in two cross-sectional studies (*43,47*). It is recommended that PrEP be made available for high-risk groups including MSM in Japan. This gap is a serious problem from a perspective of disparity in access to PrEP as well.

Despite of the absence of top-down movement, the number of PrEP users has been gradually increasing in Japan in a grass-roots way, along with an increase in the awareness of PrEP among MSM. A small pilot trial of daily PrEP of Tenofovir disoproxil fumarate (TDF)/ Emtricitabine (FTC) with 124 MSM was initiated in 2018 in Tokyo (*47*), which also contributed to prevalent information on PrEP. Since then, MSM who sought PrEP initiated access by purchasing generic TDF/FTC *via* the internet. According to a large internet-based questionnaire survey for MSM conducted in Japan in 2018, the proportion who knew about PrEP was 36.3% (1,719/4,735) (*48*); 6.8% (116/1,716) had experience in taking PrEP; 64.6% (73/113) obtained PrEP medicine *via* the internet, followed by medical institutions outside of Japan (20.4%, 23/113) and medical institutions in Japan (15%, 17/113). Importantly, only 28.1% (32/114) of PrEP users regularly see a doctor for PrEP follow-up and 43% (49/114) don't see a doctor at all. This "unsupervised use of PrEP" without necessary testing is of great concern, and providing correct information on PrEP use for high-risk groups is essential. In this respect, Kamakura *et al*. reported that 45.4% of physicians have no PrEP knowledge, according to a web-based survey that targeted physicians in specialties of treating STI and/ or HIV in Japan (*49*). People who sought PrEP follow-up tests were likely to be refused at clinics which physicians have no PrEP knowledge. There might also be a gap in knowledge about sexual minorities among medical personnel, which will be another obstacle for HIV prevention in Japan.

To prepare PrEP implementation in Japan, sexual health clinic (SHC) was established in 2017 at National Center for Global Health and Medicine in Shinjuku, Tokyo, where the one of the largest gay towns in Asia was located. The SHC is part of an ongoing prospective cohort study which, as a patient monitoring system, documents HIV and STI incidence while assessing PrEP uptake among MSM who visit the clinic. The inclusion criteria specify MSM aged 16 years or older who have had anal intercourse in their lifetime, are HIV seronegative, and provided written informed consent as described previously (*46,47*). Every three months, eligible participants received free HIV screening and testing for STIs, including early syphilis, chlamydia, and gonorrhea. Participants were given information about PrEP, but PrEP itself was not prescribed at the SHC after completion of the PrEP pilot study abovementioned. They were queried about their sexual behaviors, drug use, and PrEP status during each visit. The accumulated number of PrEP users in the cohort was gradually increased (Figure 1). The breakdown of where the PrEP initiators get PrEP medicines, in descending order, was purchase *via* the internet (62.9%, 631/1,003), clinics in Japan (19.3%, 194/1,003) and clinical trials performed in SHC (13.6%, 136/1,003). It is noteworthy that an MSM-friendly private clinic initiated generic medicine prescriptions for oral PrEP with necessary tests in 2020, which greatly contributed to PrEP access in Tokyo. Many clinics followed and more than ten clinics are providing PrEP in Tokyo at the moment. The Japanese Society for AIDS research announced the guidelines for PrEP use in 2022 in order to inform medical staffs and PrEP users of correct PrEP knowledge in response to rapidly increasing PrEP users and providers (*50*).

Disparities in PrEP implementation in Japan and challenges in the future

Though generic medicine for oral PrEP is remarkably accessible compared to brand-name drugs, expense of PrEP is fully out-of-pocket in Japan. In the SHC cohort,

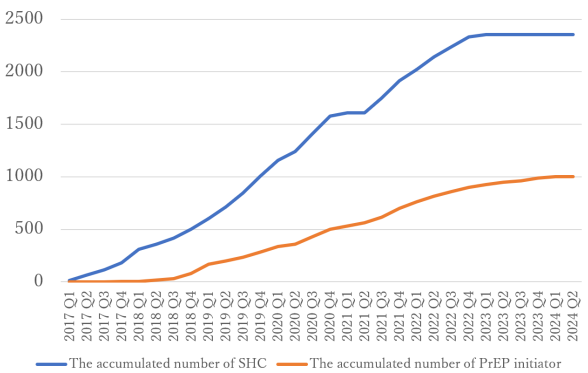

Figure 1. The accumulated number of sexual health cohort participants and PrEP initiators. Although the number of PrEP users is increasing, less than half of the participants in the cohort have not yet started PrEP. PrEP, pre-exposure prophylaxis; SHC, sexual health clinic; Q, quarter.

only half of the study participants are starting PrEP as shown in the Figure 1. The reason is multifaceted but out-of-pocket burden seems to be a main cause. According to the aforementioned survey for MSM, 87.8% (3,956/4,503) can pay less than 10,000 Japanese yen (around 60 to 70 dollars) as a monthly expense for PrEP and 54.0% (2,430/4,503) can pay less than 5,000 yen (*48*). Although some clinics offer PrEP services including HIV, other STIs, and renal function tests at around 10,000 yens at the low end, younger MSM with low or no income at greater risk of acquiring HIV infection may not afford even these reasonable PrEP services. Despite the fact that the PrEP implementation in Japan has progressed in a grass-roots way without top-down regulation and official financial support, relatively feasible access to PrEP service has been achieved. However, certain financial and geographical gaps remain.

The first gap stems from "out-of-pocket" issues which prevent people with low or no income from accessing PrEP services. It is needless to say that this disparity must be solved by official and/or other institutional supports. The second gap is a geographical disparity inside Japan in which MSM living outside of Tokyo have much more limited access to PrEP services compared to MSM living in Tokyo. This geographical matter is also the case with the awareness of PrEP. Under the current situation of PrEP provision in Japan, purchasing generic medicines for PrEP *via* the internet can be an option to mitigate this disparity. However, low awareness of PrEP outside of Tokyo contributes to low numbers of internet-based purchase of PrEP. Furthermore, those who purchase internet-based PrEP must seek out testing on their own, and lower knowledge among physicians outside of Tokyo is a challenge. HIV and syphilis tests regularly provided by public health centers will be a part of the solution, though the capacity of these centers depends on each area. One of the important problems in HIV prevention in Japan is that the testing strategy performed in the public health centers and municipalities does not include treatments and preventive intervention like PrEP, since public health centers are not regulated to prescribe but provide only consultation and testing. As PrEP is not approved at the moment, quite few public health centers are involved in PrEP services. However, recently, public health centers in some areas are entrusting their HIV and other STI testing tasks to MSM friendly clinics, which may not only mitigate shortage of human and financial resources but coordinate tests, treatments, and prevention strategies.

It is essential to improve awareness of PrEP among the involved people including medical staff in Japan. In this respect, approval of PrEP will allow for dissemination of correct information on PrEP. The efficacy and benefit of PrEP are evident in a number of countries. In Japan, high efficacy was reported as well. According to the aforementioned pilot study, HIV incidence rate was significantly higher in the non-PrEP users compared to the PrEP users (3.45/100 *vs.* 0 person-years, $p = 0.01$) (*47*). In terms of cost-effectiveness analysis, two studies demonstrated PrEP as a cost-saving strategy in Japan (*51,52*). It is of note that the current situation of bottom-up PrEP implementation using much cheaper generic medicines in Japan is obviously cost-saving, which is needless to evaluate. In addition to the approval of PrEP, official financial support for PrEP is required; otherwise, authorities in charge will be regarded as free-riders. At the least, the current path of PrEP system that occurred in a grass-roots manner should be paved by authorities without impairing existing virtues of accessibility and cost-saving.

Conclusions and Future directions

Regarding UNAIDS's 95-95-95 HIV testing and treatment cascade, there is room for improvement in the first and second 95, namely, proliferation of HIV testing and early initiation of treatment. However, the largest gap to be filled is the delay in PrEP implementation. Without official support for PrEP, grass-roots PrEP implementation based on user-friendly clinics has been functioning well in some areas like Tokyo. However, there are geographical and financial disparities in access to PrEP services. To establish a more accessible, cost-saving and equitable PrEP system, current existing but isolated entities and strategies related to HIV management needs to be integrated and coordinated with other. In this respect, the role of the authorities is important to close the gaps in PrEP implementation.

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