

Forty years of HIV infection and AIDS in Taiwan: Reflection on the past and looking toward the future

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ABSTRACT

We review the epidemiology, policies, and control programs of HIV infection in Taiwan in the past 40 years since the first case of HIV infection was diagnosed in 1984. With the introduction of combination antiretroviral therapy (ART) in Taiwan in 1997, the incidences of HIV-related opportunistic illnesses and mortality have significantly declined. However, despite improved access to HIV testing and treatment, late presentation of HIV infection remains common. Unprotected sex, particularly among men who have sex with men, continues to be the leading risk for HIV transmission after implementation of harm reduction program to control an outbreak of HIV infection among people who inject drugs that occurred in 2003–2007. The sequential introduction of well-tolerated, effective, single-tablet antiretroviral regimens has facilitated the implementation of “treat-all” policy in 2016, rapid ART initiation within 7 days of diagnosis in 2018, and same-day ART initiation in 2021 when immunochromatography was used for rapid confirmation of HIV infection. Government-funded pilot program of pre-exposure prophylaxis for HIV infection, which was launched in 2016 followed by wider enrollment of people at high risk for HIV acquisition in 2018, have contributed to sustained declines of the incidence of HIV infection since 2018, along with high rates of linkage to HIV care, ART initiation, viral suppression, and retention in care in Taiwan. Challenges remain to achieve HIV elimination and long-term successful management of HIV infection, which include stigma and discrimination, late presentation of HIV infection, and accelerated ageing with increasing rates of co-morbidities among people with HIV.

1. Introduction

Since the first case of HIV infection was diagnosed in Taiwan in 1984, a total of 44,263 autochthonous cases were reported to Taiwan Centers for Disease Control (CDC) by the end of 2023, among whom 21,585 (48.8%) were diagnosed with AIDS and 8510 (19.2%) died. Meanwhile, 35,566 people were living with HIV in Taiwan, representing an estimated prevalence of 0.1% of the population. To control the HIV epidemic, Taiwanese government implemented programs of HIV testing

and introduced well-tolerated, effective combination antiretroviral therapy (ART), immunochromatographic test (ICT) to facilitate rapid and same-day ART initiation, and pre-exposure prophylaxis (PrEP). Here, we review the evolution of HIV epidemiology, policies, and control programs implemented for the control of HIV epidemic in the past 40 years, and examine the challenges ahead to achieve elimination of HIV infection as a public health threat and long-term successful management of HIV infection in Taiwan.

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2. Epidemiology of HIV infection in Taiwan

The first imported case of HIV infection in Taiwan was reported in 1984^{1,2} and the first locally acquired case in 1986.³ Subsequently, the incident case number of people with HIV (PWH) continued to increase in the next 34 years and transmission routes have evolved over time (Fig. 1). The initial wave of HIV infections in the early 1980s was caused by transfusion of contaminated antihemophilic products that had resulted in at least 53 cases of HIV infection.⁴ The first case of blood transfusion-related HIV infection probably occurred in 1985 in a woman who received HIV-1-positive whole blood transfusion during hysterectomy.⁵ With the implementation of routine blood donor screening in 1988 (Fig. 2) and incorporation of nucleic-acid amplification test (NAAT) as a screening method in 2013, no cases of transfusion-related HIV transmission occurred after 2014.⁶

During the first two decades of HIV epidemic in Taiwan, male-to-male unprotected sex was the predominant route of HIV transmission. From 2003 to 2007, there was an outbreak of HIV infection among people who inject drugs (PWID), with the proportion of PWID among annually reported cases rising from 1.7% in 2002 to >75% in 2005.⁷ Molecular epidemiology studies linked the epidemic among PWID to HIV CRF07_BC that used to circulate among PWID in China.^{7–11} A high prevalence of hepatitis C virus (HCV) infection among HIV-positive PWID was also observed.^{12,13} Following the implementation of harm reduction program in 2005, notable declines in HIV infection have been observed among PWID.^{14,15} Thereafter, unprotected sexual contact, particularly male-to-male (67%) and heterosexual (15%) contact, became the predominant transmission route.^{16,17}

By the end of 2023, 94.9% of the reported cases of HIV infection in Taiwan were male and the majority were aged between 25 and 34 years at the time of their HIV diagnoses (43.3%), followed by those aged 35–49 years (26.3%) and 15–24 years (23.4%). The proportion of PWH aged 15 years or less remained low, accounting for 0.14% of all PWH diagnosed. The first case of perinatal transmission of HIV was reported in 1988.¹⁸ After implementing routine (opt-out) HIV testing for pregnant women in 2005, mother-to-child transmission of HIV had become a rare occurrence.^{19,20} Between 2015 and 2023, 8 cases of pediatric HIV infection were reported, including infants vertically infected by their mothers who did not adhere to antenatal care and adolescents infected through sexual contact.

Due to implementations of screening programs and biomedical intervention for HIV infection, Taiwan has made significant progress towards achieving the UNAIDS “95-95-95” targets, with the targets reached progressing from “71-62-81” in 2012, “84-88-94” in 2018, to “91-96-95” in 2023.²¹ Consequently, the incidence of HIV infection has been declining for six consecutive years (since 2018) and has reached to an annually reported number of 940 (4.1 persons per 100,000

population) in 2023. While the percentage of undiagnosed infections in gay, bisexual, and other men who have sex with men (GBMSM) population sharply decreased, a significant gap remains in achieving the first 95% target and higher proportions of undiagnosed infections were observed among heterosexuals and younger individuals aged between 15 and 24 years.²²

Despite the advancements in HIV testing, ART coverage, and viral suppression rates, late HIV diagnosis and sexual transmission of HIV still pose considerable challenges to HIV control and care delivery in Taiwan. Annually, more than 30% of PWH in Taiwan were identified at an advanced stage of the disease (progression to AIDS within 3 months after receiving HIV diagnosis), with the rate increasing to over 35% since 2019.²³ Late HIV diagnosis leads to delayed initiation of ART, thereby increasing the risk of poor clinical outcomes and ongoing HIV transmission.^{24,25} In individuals with late diagnosis of HIV infection, oro-esophageal candidiasis and *Pneumocystis jirovecii* pneumonia continued to be the most common AIDS-defining opportunistic infections.²⁶ Several factors have been identified as significantly associated with late HIV diagnosis, including older age, having non-fixed sexual partners, and being diagnosed due to symptoms rather than through routine screening.²⁷ These findings emphasize the importance of information and education delivered to the general population and health care providers, regular risk assessment, routine provision of HIV testing during medical encounters, and improving accessibility to voluntary HIV testing.²⁸ While the stigma and discrimination linked to an HIV diagnosis hamper access to HIV screening and care among vulnerable populations, expanding HIV testing to achieve early HIV diagnosis has been shown to be highly beneficial, resulting in gains in healthy life years.²⁹

The prolonged sexually transmitted HIV outbreak, primarily transmitted through unprotected sexual contact among GBMSM, could be linked to the use of non-opioid recreational drugs.³⁰ Given the established association between drug use in sexual contexts (chemsex) and HIV among GBMSM, tailored harm reduction strategies are needed to achieve elimination of HIV infection. These strategies should go beyond traditional programs and include mental health services, drug use management and recovery support, as well as the provision of GBMSM with community-based health services.^{31,32}

3. Law and policy in Taiwan

During the 40 years of HIV epidemic, prevention and control policy development has evolved from proactive health education, contact tracing, and interventions to increase ART coverage towards improvement of access to testing and care, partner services, harm reduction programs, prevention of mother-to-child transmission, and PrEP.³³ Establishing communication and coordination mechanisms between

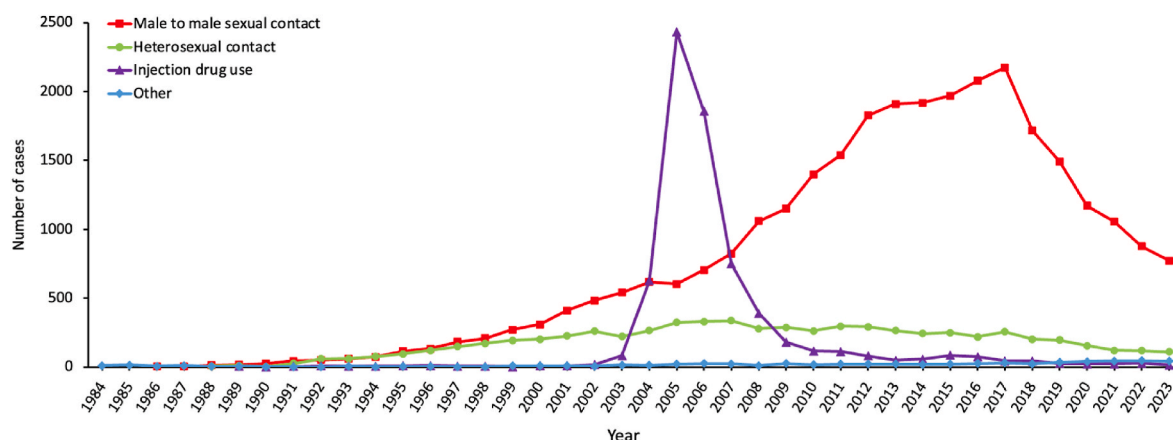


Fig. 1. Trend of incident HIV infections by transmission category in Taiwan, 1984–2023.

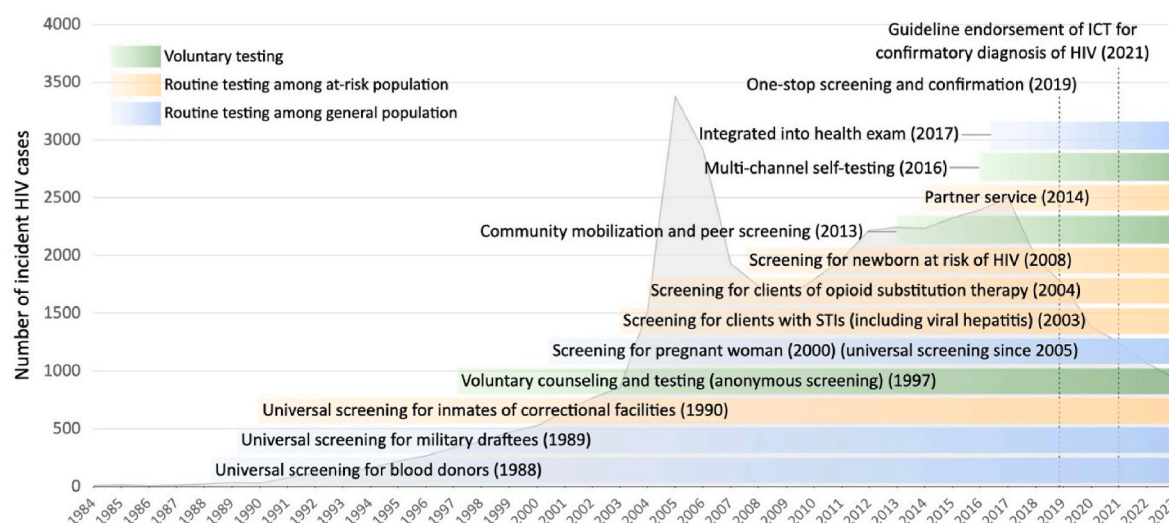


Fig. 2. Progress in HIV screening services amidst the evolution of HIV epidemic in Taiwan, 1984–2023. Abbreviations: ICT, immunochromatography test; STI, sexually transmitted infection.

government agencies and community-based organizations (CBOs) to improve public-private collaboration has resulted in successful public participation, which has enabled various issues and policies to be effectively communicated and implemented through multisectoral and committee mechanisms, thereby creating a friendly and non-discriminatory environment for PWH.

To facilitate comprehensive assessment of the law and policies implemented for HIV control and human rights protection in Taiwan in the past four decades, we examined the accomplishment using the HIV policy indicators developed by the HIV Policy Lab,³⁴ in which there are four categories, including clinical/treatment, testing/prevention, structural, and health systems, and 33 indicators (Supplementary Table 1).

In the 1980s–1990s when panic and stigma were prevalent due to a lack of understanding about HIV, the society at large harbored fear and discrimination against PWH, associating the virus with certain risk groups (such as gay men and injection drug users). In 1988, Taiwan started to provide free zidovudine (AZT) and HIV care to PWH at designated hospitals (Fig. 3), followed by enactment of the AIDS Prevention and Control Act in 1990, which provided legal grounds for HIV testing and treatment and privacy protection for PWH. Mandatory testing was also imposed on perceived high-risk groups, raising human rights concerns at the time. In the early years of HIV epidemic, foreigners entering or residing in Taiwan for more than three months were

required to undergo HIV testing and those found to be HIV-positive were subject to deportation, which had resulted in instances where foreign spouses of Taiwanese nationals found to be PWH had to face forced deportation. Subsequently, these restrictions were gradually lifted to uphold legitimate partner relationships and adhere to humanitarian principles.³⁵

In the 1990s to 2010, it was the times of transition from disease control to human rights protection. While the government continued to emphasize disease prevention and control, discrimination against PWH remained widespread. In 1994, a school child who contracted HIV through blood transfusion was forced to transfer schools, prompting the 1997 revision of laws to protect the rights of PWH in accessing medical care, education, and employment. In the same year (1997), combination ART was introduced.³⁶

When the HIV epidemic occurred among PWID occurred in 2003 and reached its peak in 2005 (Fig. 1), the government sought advice from foreign experts to develop harm reduction programs. A pilot program, including needle and syringe exchange and health education, was started in four of 23 administrative areas in Taiwan in July 2005, and opioid substitution therapy (OST) was introduced in February 2006^{15,37}, which became legalized in 2007.

To enhance care and support for PWH, Taiwan initiated the pilot program of HIV case management, which was subsequently implemented nationwide in 2007.³⁸ Initially focusing on hospital-based

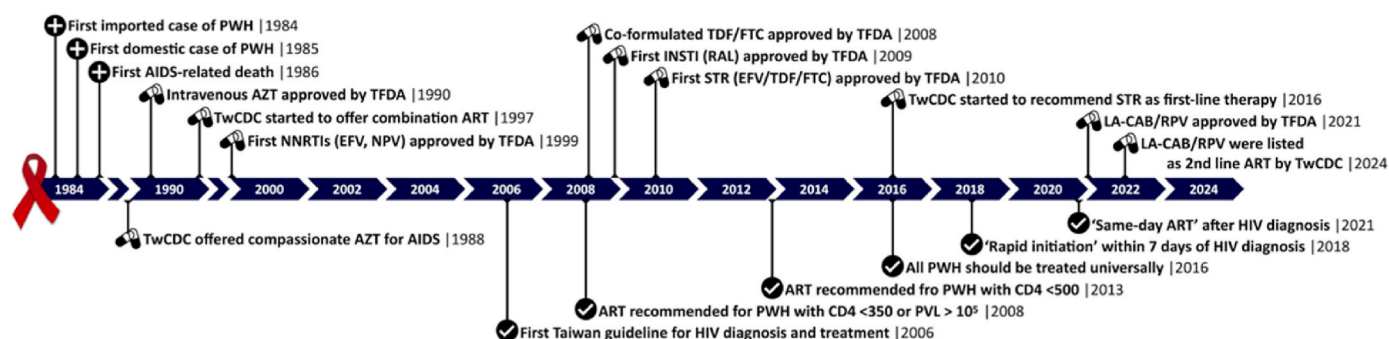


Fig. 3. Evolution of antiretroviral therapy and treatment strategies over the past four decades in Taiwan.

Abbreviations: ART, antiretroviral therapy; AZT, zidovudine; CAB, cabotegravir; EFV, efavirenz; FTC, emtricitabine; INSTI, integrase strand-transfer inhibitors; LA, long-acting injectables; NNRTIs, non-nucleoside reverse-transcriptase inhibitors; NPV, nevirapine; PVL, plasma HIV RNA load; PWH, people with HIV; RAL, raltegravir; RPV, rilpivirine; STR, single-tablet regimen; TDF, tenofovir disoproxil fumarate; TFDA, Taiwan Food and Drug Administration; TwCDC, Taiwan Centers for Disease Control.

management, this program aimed to improve adherence to ART to achieve durable viral suppression among PWH.^{39,40} Presently, CBOs have assumed a more prominent role, particularly in providing support to disadvantaged PWH, adolescents, and those engaged in chemsex.³²

In 2007, in response to cases in which CBOs housing socio-economically disadvantaged PWH faced social exclusion from their neighborhoods, both public and private care institutions were explicitly prohibited from refusing to admit PWH to protect their rights to care and residence. Furthermore, measures were implemented to safeguard the rights of PWH, including the establishment of a framework where advocacy groups, CBOs, public health experts, health care providers, and representatives from relevant government agencies collaborated to promote HIV prevention and protect the rights of PWH. In the same year, the legislation was renamed the HIV Infection Control and Patient Rights Protection Act, reflecting that its legislative purpose extended beyond the original objectives of disease prevention to encompass human rights protection.

From 2010s to the present, a period marked by a shift from opposition to collaboration, PWH continue to face discrimination despite improved legal protections. In 2013, a university student with HIV was expelled, drawing public attention to HIV-related discrimination and prompting further reflection by human rights groups on the treatment of PWH. In 2015, Taiwan abolished its entry ban on foreigners with HIV, aligning its policies with global trends of increasing inclusivity and respect for human rights. By 2019, the rise of the gender equality movement and the legalization of same-sex marriage further advanced the social acceptance of HIV-related and gender issues. In 2020, a legal revision clarified that PWH who were on stable ART and had achieved viral suppression posed no significant risk of HIV transmission, thus exempting them from being classified as engaged in “risky sexual behavior” and encouraging PWH to adhere to treatment without fear.

With regard to other major policies, Taiwan followed the WHO guidelines to implement ART initiation for all PWH in 2016, regardless of CD4 count or AIDS status²⁴; and rapid ART initiation and same-day ART initiation were implemented in 2018 and 2021, respectively. PrEP pilot program was started in 2016 and has been expanded to increase the coverage of people at risk for HIV infection since 2018.⁴¹ The national HIV self-testing program was implemented in 2017,⁴² which has been demonstrated to improve HIV case finding.

In order to reduce stigma or discrimination, the framework of The First Phase Plan to Eliminate HIV/AIDS by 2030 was divided into five levels, including governmental/structural, community, organizational/institutional, interpersonal, and intrapersonal.^{33,43} Strategies included health education, universal testing, promotion of the updated evidence of U=U (undetectable=equals-untransmittable), training programs targeting different subgroups of multisectoral organizations and CBOs, and subsidies for HIV-designated hospitals and CBOs to develop group counseling or support groups.

At the end of 2023, an estimated 9% of PWH in Taiwan remained undiagnosed, strategies to promote routine HIV screening and to provide client-centered HIV testing are ongoing and will be discussed in the next section. Moreover, 4% of those with a known HIV diagnosis were not engaged in care, and 5% of PWH who had started ART failed to achieve viral suppression, potentially leading to ongoing transmission risks in the community. Sustainable resources will need to be invested to strengthen the system's ability to maximize and maintain the level of retention in treatment and prevention services.

4. Progress in HIV screening and diagnosis

HIV screening, which triggers subsequent confirmation of HIV diagnosis and treatment or preventive measures, plays a critical and fundamental role in HIV control programs. In response to the HIV pandemic, Taiwan started its routine HIV screening first among blood donors in 1988,⁵ military draftees in 1989, and inmates in 1990 (Fig. 2).⁴⁴ In the following decades, Taiwan has witnessed a

comprehensive expansion of screening initiatives, which included screening programs among pregnant women, clients with sexually transmitted infections (STIs), PWID enrolled in OST programs, and at-risk newborns since 2000, 2003, 2004, and 2008, respectively.⁴⁴

Free anonymous voluntary counseling and testing (VCT) was first provided at a few healthcare facilities since 1990, and a nationwide anonymous VCT program was initiated in 1997 at several hospitals, clinics, and CBOs aiming at providing HIV screening and counseling services that were friendly, accessible, and safe to at-risk clients.^{45,46} The services proved to be effective in identification of clients at risk for HIV infection, as the HIV seroprevalence and the prevalence of concomitant STIs were high among this group of individuals (HIV seroprevalence up to 3.6–4.1%).^{45,47} Moreover, the proportion of cases of new HIV diagnosis identified by anonymous VCT services had increased from 5.2% to 29.3% from 2005 to 2016. In the past decade, innovations on HIV testing such as community mobilization, multi-channel self-testing services,⁴² and mobile VCT through social networking platforms⁴⁸ showcased the nation's commitment to increasing HIV testing coverage.

With these collective efforts, the annual number of HIV screening tests provided each year had reached 833,843 in 2019, which dropped to 667,133 in 2020 during the COVID-19 pandemic and slowly climbed back to 721,436 after the pandemic in 2023,²³ and the proportion of PWH who were undiagnosed had been on the decrease (21.5% in 2012, 12.1% in 2019, and 9% in 2023).^{22,23} The lingering disparity in attaining the first “95” target could be attributed to underestimation of HIV risk, stigma, fear of discrimination, and lack of accessible preventive information in specific populations (females, transgender people, migrant workers, elderly, and adolescents).^{46,49,50} Other than efforts to improve public education and communication, implementation of additional novel channels for HIV screening are also ongoing, including peer screening, partner services, and integrated HIV screening into routine health examination. Universal screening was advocated for all people with sexual experience by Taiwan CDC to de-stigmatize HIV testing and to improve coverage. A recent analysis showed that the implementation of routine HIV testing in Taiwan was associated with a decreased rate of late diagnosis and lower HIV-related mortality and all-cause mortality.²⁸ Such findings support further expansion of universal, opt-out testing to broader settings, although the practicability and cost-effectiveness remain to be examined in Taiwan.

In the past decades, the tools for HIV screening have evolved, progressing from 2nd generation tests that used recombinant antigen, to 3rd generation enzyme immunoassay/particle agglutination assays (EIA/PA) that incorporated IgM detection, and then to the 4th/5th generation that adds p24 antigen in the antigen/antibody combination tests, which significantly shortens the window period. The introduction of ICT in 2019 had facilitated one-stop screening and confirmation of HIV infection. The endorsement of NAAT and ICT for confirmation of HIV diagnosis in the Taiwan CDC guidelines in 2021,⁵¹ replacing traditional Western blot assay, have significantly reduced the turnaround time for HIV confirmation and expedited the linkage of people newly diagnosed with HIV to care and ART initiation.⁵²

Testing of antiretroviral resistance of HIV-1 at the time of ART initiation was not performed routinely in Taiwan and is not reimbursed by the National Health Insurance (NHI). While genotypic resistance testing at the time of treatment failure is recommended by national treatment guidelines, resistance testing and surveillance provided by several research laboratories in Taiwan play a pivotal role in policy-making and in guiding ART prescription in both antiretroviral-naïve and antiretroviral-experienced PWH.^{53–56} Notably, increases in the prevalence of pre-treatment drug resistance (PDR) to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) have been observed in several surveillance studies.^{57,58} In a study that included around 25% of antiretroviral-naïve PWH during 2016–2022, the prevalence of PDR to 1st generation integrase strand-transfer inhibitors (INSTIs) (i.e. elvitegravir and raltegravir) had increased from 1.1% at 2016 to 3.6% at

2022, while the prevalence of PDR to 2nd generation INSTIs (dolutegravir, bictegravir, and cabotegravir) was stable at around 1%.⁵⁹ Other studies also showed that resistance to INSTIs among PWH who were naïve to INSTIs remained uncommon (Table 1).^{55,58–60} As intermediate- or high-level resistance to second-generation INSTIs has emerged in different countries,^{61,62} surveillance of antiretroviral resistance in Taiwan should be continued and policies should be implemented to improve its access and sustainability.

5. Evolution of ART treatment strategies

In the past three decades, ART has been demonstrated to suppress HIV replication, prevent onward transmission, and reduce disease progression among PWH. National ART treatment strategies have evolved since 1988, when compassionate use of AZT for AIDS was first provided (Fig. 3). In the mid-1990s, like other developed countries, ART in Taiwan comprised one or two different nucleoside reverse-transcriptase inhibitors (NRTIs). In 1997, Taiwan CDC updated its treatment guidelines by providing free-of-charge, multi-tablet ART consisting of two NRTIs plus one NNRTI or boosted or unboosted protease inhibitor (PI) to all Taiwanese PWH. Subsequently, the survival of PWH in Taiwan has significantly improved and opportunistic illnesses decreased in the modern ART era.^{36,63–65} Primary and secondary prophylaxis for several opportunistic infections could be discontinued when CD4 count increased and viral suppression was achieved.^{66–69}

A significant shift in the ART history in Taiwan occurred in 2016, when the first single-tablet regimens (STRs), co-formulated tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/efavirenz, was introduced. Subsequently, TDF/FTC/rilpivirine (RPV), abacavir/lamivudine (3TC)/dolutegravir (DTG), tenofovir alafenamide (TAF)/FTC/RPV, TAF/FTC/cobicistat-boosted elvitegravir, DTG/RPV, TAF/FTC/bictegravir (BIC), and DTG/3TC were sequentially introduced and recommended as the first-line treatment or as stable switch regimens. Within a decade, STRs have become the mainstay of ART in Taiwan, relegating multi-tablet regimens to selected PWH with antiretroviral resistance or intolerance.

Because of increased PDR of HIV-1 to NNRTIs, which exceeded 10% in several surveillance studies (Table 1),^{53,59,70} STRs containing second-generation INSTIs, DTG or BIC, have emerged as the primary treatment options for both antiretroviral-naïve and antiretroviral-experienced PWH in the past decade. In 2021, Taiwan Food and Drug Administration approved the first long-acting (LA) injectable antiretrovirals, and the combination of LA-cabotegravir and

RPV was listed as a second-line ART by Taiwan CDC in 2024.

Alongside the advancements in ART, the indications and timing for initiation of ART have also evolved significantly over time. A pivotal shift occurred in 2016, when ART was recommended for all PWH upon confirmed HIV diagnosis, moving away from previous criteria that relied on CD4 lymphocyte counts or plasma HIV RNA loads to initiate ART (Fig. 3). Thereafter, Taiwan CDC switched its focus towards minimizing the delay between HIV diagnosis and ART initiation. By 2018, hospitals designated for HIV care around Taiwan were advised to offer rapid initiation of ART, aiming to start ART within 7 days of a confirmatory HIV test for newly diagnosed PWH.^{52,71} Similar to studies in other parts of the world, real-world evidence in Taiwan also suggested that PWH on rapid ART initiation were more likely to be engaged in care and less likely to become lost to follow-up compared to PWH who initiated ART ≥7 days after a confirmed HIV diagnosis.⁷² To further improve the linkage of people newly diagnosed with HIV infection to care, Taiwan CDC implemented same-day ART initiation program in 2021, in which ART initiation on the same day of a confirmed HIV diagnosis was advised. With the increased utilization of ICT or NAAT,^{72,73} the median interval from a positive HIV screening test to initiation of ART has been reduced to just one day by 2023, with more than 60% of newly diagnosed PWH initiating ART within the first two days of testing positive on HIV screening.⁵²

As of today, STRs consisting of second-generation INSTIs have significantly improved tolerability, provide a higher genetic barrier to resistance, and demonstrate remarkable effectiveness in real-world settings in Taiwan.^{74,75} However, it is critical to acknowledge that a small proportion of PWH still face challenges with adherence, risking treatment failure and emergence of resistance-associated mutations of HIV-1. For instance, PWH who use recreational drugs or PWID are recognized as having lower adherence rates. Moreover, there is growing international evidence that suggests emerging resistance to second-generation INSTIs is still a possibility, especially among PWH with non-adherence.^{61,62}

6. Pre-exposure prophylaxis

Since September 2015, WHO has adopted oral PrEP with TDF-based regimen as part of comprehensive prevention for populations at substantial risk of HIV infection.⁷⁶ Taiwan AIDS Society published the first version of national PrEP guidelines in May 2016, recommending GBMSM and transgender women, HIV-negative partners in a sero-discordant relationship, sexually-active heterosexual cisgender men and

Table 1
Pretreatment drug resistance of HIV-1 observed in different published studies among antiretroviral-naïve people with HIV in Taiwan.

Authors and journal	Study years	Sample size	Prevalence of ARV resistance				
			NRTI	NNRTI	PI	INSTI	INSTI mutations
Chang SY et al. JAC (2008) ⁵³	1999–2003	424	4.5%	2.8%	1.2%	NA	
	2004–2006	362	6.1%	5.5%	4.4%	NA	
Lai CC et al. JAC (2012) ⁵⁴	2000–2010	1349	3.8%	3.6%	2.2%	NA	
Chang SY et al. Scientific Reports (2016) ⁵⁵	2006–2015	948	NA	NA	NA	0.6%	Q148QR (0.5%) Y143R (0.1%)
Weng YW et al. BMC Infect Dis (2019) ⁵⁶	2007–2011	161	3.1%	8.7%	0%	0%	
	2012–2015	216	2.3%	6.5%	0%	0%	
Tsai HC et al. Infect Drug Resist (2022) ⁵⁷	2013–2016	208	4.0%	6.4%	0%	1.1%	R263K (0.5%) G163R (0.5%) G163R (1.3%) G163K (0.7%) E157Q (1.3%) E138A (0.7%)
	2017–2021	161	2.5%	7.5%	0%	2.6%	G163K (0.6%) D232N (0.6%) G163 K/R (1.7%) R263K (0.1%) N155H (0.1%) Q148 H/K/R (0.1%)
Huang SW et al. JAC (2021) ⁵⁸	2018–2020	164	1.3%	21.0%	1.9%	1.3%	
Chen GJ et al. JAC (2024) ⁵⁹	2016–2022	3001	2.1%	10.0%	0.4%	2.5%	

women as well as PWID to take daily TDF/FTC as PrEP. Several updates have been made since, including recommendation on event-driven dosing regimen in May 2018, and other novel agents such as fixed-dose combination of TAF and FTC, long-acting cabotegravir intramuscular injection, and dapivirine vaginal ring in September 2023.^{77,78} (Fig. 4)

Local studies have also shown that, compared to other at-risk populations in Taiwan, GBMSM were significantly more aware of and willing to initiate PrEP, especially among those who perceived a high susceptibility to HIV infection, but few would like to pay out-of-pocket to buy branded TDF/FTC for PrEP.^{79–81} Event-driven PrEP has been chosen preferably by Taiwanese GBMSM, and switching between event-driven and daily dosing regimens is not uncommon.^{82–84} Regarding long-acting PrEP options without considering the cost, Taiwanese GBMSM currently taking PrEP prefer monthly oral PrEP, followed by a six-month subcutaneous injection, and then a bimonthly intramuscular injection in one survey.⁸⁵

Meanwhile, Taiwan CDC launched the pilot PrEP program aiming to enroll 1000 participants in 5 hospitals in November 2016, which also served as the first government-funded PrEP program in Asia. The pilot program came to a halt due to opposition by religious conservatives in September 2017, resulting in enrollment of less than one third of the target number, although the preliminary result showed an excitingly low HIV seroconversion rate (0.3%) among the participants.⁸⁶ To further expand PrEP coverage, scale-up programs have been implemented by Taiwan CDC since September 2018, providing government-funded TDF/FTC to young adults aged below 30 years, serodiscordant couples, commercial sex workers, and people with sexualized drug use.⁴¹ The programs were rolled out with integrated sexual health services including HIV self-testing, one-stop testing and treatment, Mpox vaccination, and chemsex intervention. As of December 2023, there have been more than 5700 people enrolled in the government-funded PrEP programs at 63 hospitals and clinics around Taiwan. The programs also demonstrated protection against HIV acquisition for individuals with STIs and participants who retained in the programs.⁴¹ (Fig. 4)

Nevertheless, unlike treatment for HIV infection, preventive measures such as PrEP have been left uncovered by the highly acclaimed,

universal NHI in Taiwan, not as in the case of National Health Service in the United Kingdom.^{87–90} In addition, generic forms have yet to be available even though the patent of branded TDF/FTC expired in 2020. While the uptake of PrEP among at-risk populations from government-funded programs has gradually increased, GBMSM who are not eligible or have no access to these programs keep seeking out-of-pocket generic TDF/FTC from “gray market” on the internet or pharmacies in the neighboring countries in Asia.⁸⁶ The true number of current PrEP users in Taiwan is likely to be underestimated, and hence, the actual impact of PrEP on the recent decline of HIV incidence needs to be elucidated. Removal of the financial barriers to affordable PrEP for all remains the greatest challenge to further expand its coverage in Taiwan.

7. Beyond viral suppression: HIV comorbidities and holistic care

With the above-mentioned progress in HIV testing and care, PWH nowadays have extended longevity, approaching that of general population.⁹¹ In 2023, PWH aged over 50 years accounted for 23% of all PWH in Taiwan. While deaths attributable to AIDS-related diseases have declined from 31 % in 2014 to 11% in 2023 in Taiwan,²³ PWH are at a higher risk for comorbidities including hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, renal disease, and reduced bone mineral density, as compared to people without HIV.^{92,93} One single-site study in 2008 and 2009 showed nearly a quarter of Taiwanese PWH had metabolic syndrome.⁹⁴ In a cross-sectional study investigating PWH aged 40–75 years, the prevalence of high cardiovascular disease risk varied, ranging from 3.7% by D:A:D (R) risk score, and 22.2% by Atherosclerotic Cardiovascular Disease risk score, to 30.6% by Framingham Risk Score.⁹⁵ Increased comorbidities have posed challenges to PWH and the healthcare system. In one study analyzing data from NHI Research Database (NHIRD), the overall spending on medications for comorbidities among PWH nearly doubled from 2010 to 2013.⁹⁶

The increased risk for comorbidities among PWH could be attributable to multiple factors, including gene, age, lifestyle, smoking, chronic inflammation, and antiretroviral agents. The impact varied among different classes of antiretroviral agents across the published studies. Real-world data in Taiwan demonstrated mild weight gain and

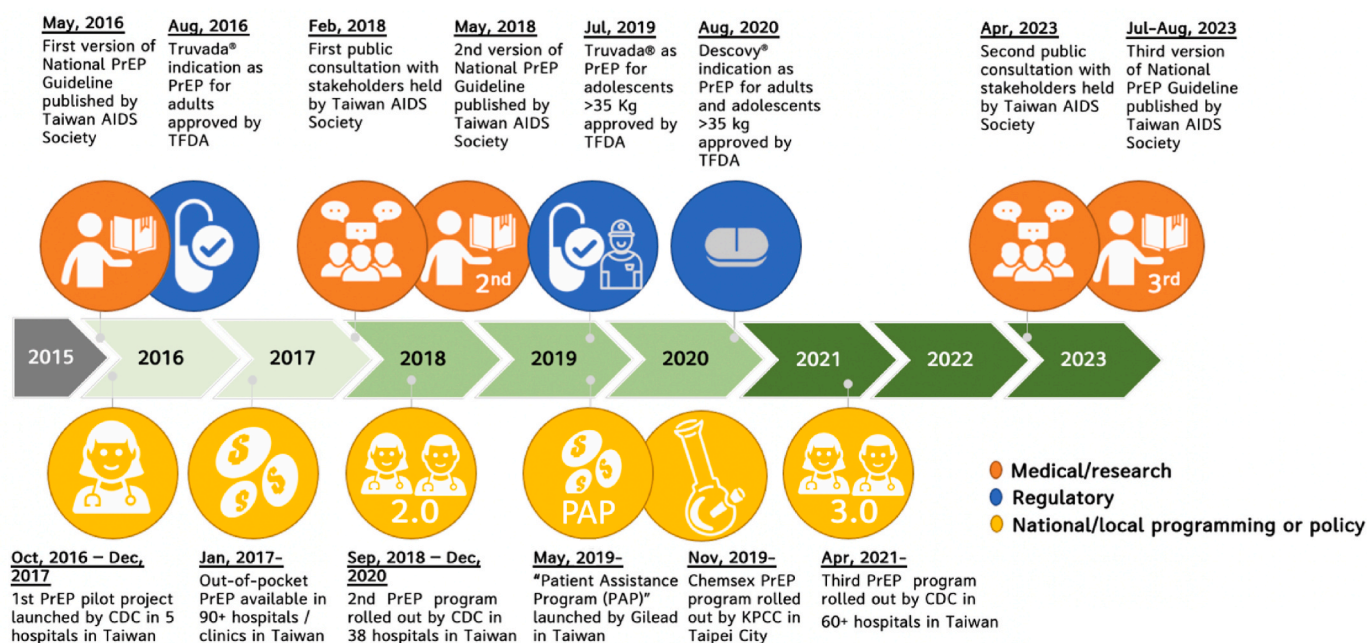


Fig. 4. Timeline of pre-exposure prophylaxis implementation in Taiwan.

Abbreviations: CDC, Taiwan Centers for Disease Control; PrEP, pre-exposure prophylaxis; TFDA, Taiwan Food and Drug Administration; KPCC, Taipei City Hospital Kunming Prevention and Control Center.

dyslipidemia for virally suppressed PWH switching to INSTI-based regimens.^{75,97} While statins as primary prophylaxis have been shown to significantly reduce major adverse cardiovascular events among PWH at low or moderate risk,⁹⁸ they were underutilized in the clinical practices; for example, only less than 40% of PWH who met the criteria for statin use according to the recommendations of American Heart Association received statins during their HIV care at a university hospital,⁹⁹ suggesting that comprehensive measures to prevent cardiovascular diseases have yet to be integrated in the HIV care services in Taiwan.

Sexually active PWH are at ongoing risk for STIs, including syphilis, *Chlamydia trachomatis* infection, gonorrhea, trichomoniasis, *Mycoplasma genitalium* infection, and human papilloma virus (HPV) infection. In one Taiwanese study, the overall prevalence for chlamydia, gonorrhea, and/or trichomoniasis was 30% among PWH.¹⁰⁰ Another study demonstrated 32.9% of concomitant bacterial infections in HIV-positive MSM who presented with STIs.¹⁰¹ One study investigating anosopic specimens showed 90.8% of the participants had infections with at least one HPV genotype.¹⁰² Preventive measurements including safe sex practice, health education, and vaccination (e.g., HPV vaccination) should be promoted to manage the STIs syndemics. Doxycycline for post-exposure prophylaxis against bacterial STIs have been proven effective in reducing the risk for chlamydial infection, syphilis, and possibly gonorrhea in recent randomized trials.^{103,104} While the impact of wider use of doxycycline on the carriage of bacteria with emergent resistance to doxycycline and the intestinal microbiota remain to be studied, discussion about prevention of bacterial STIs with doxycycline should be promoted.

As a country with hyperendemicity of hepatitis B virus (HBV) infection, the overall prevalence of HBV infection in Taiwan was 11.6% between 2012 and 2016.¹⁰⁵ The prevalence has decreased significantly from 18.1% to 3.4% among PWH born before and those after 1986, when nationwide universal neonatal HBV vaccination program was implemented.¹⁰⁵ For people with HIV/HBV coinfection, ART containing TDF or TAF is recommended. Taiwanese studies demonstrated significant mortality reduction among people with HIV/HBV coinfection after the introduction of TDF in 2011¹⁰⁶ and durable effectiveness in controlling HBV replication with TDF- and TAF-containing regimens in this population.^{107–109} Despite nationwide vaccination at neonatal stage, serological protection may wane gradually and incident HBV infections may occur in at-risk populations despite use of ART containing TDF or TAF.¹¹⁰ Studies showed modest serological response of 74.0% after a 3-dose revaccination.¹¹¹ Periodic serological evaluation and HBV booster vaccination among seroreverters are recommended.¹¹²

Hepatitis D virus (HDV) was associated with increased risk of adverse hepatic outcomes and mortality among people with HIV/HBV coinfection.¹¹³ The incidence of recent HDV infection increased significantly from 1992–2001 to 2007–2011 in one single-center study.¹¹⁴ A recent study showed an overall incidence rate of 12.65 per 1000 person-years of follow-up.¹¹⁵ Due to limitations of diagnosis and treatment, HDV coinfection is likely underdiagnosed. As newer diagnostics and treatment options emerge, surveillance of HDV superinfection among people with HIV/HBV coinfection is warranted, especially among PWID due to their higher risk of HDV infection.¹¹⁶

To achieve the goal of HCV elimination by 2025, direct-acting antivirals (DAAs) have been reimbursed by NHI in Taiwan since 2017. Barriers to elimination included suboptimal diagnostic approach, incomplete treatment linkage, and high reinfection rate among key subgroups. In one retrospective study, 74.9% of PWH with HCV viremia initiated anti-HCV treatment and 94% of these individuals achieved viral clearance.¹¹⁷ Compared to people without HIV, PWH have a higher risk of HCV reinfection.¹¹⁸ After implementation of DAA treatment program, the prevalence and incidence of HCV have declined while the proportion of reinfections increased among PWH.¹¹⁹ Recent studies suggested diagnostic strategies with more frequent screening and pooled-plasma HCV RNA testing may help to identify acute HCV infection timely^{120,121} and the latest data showed the rate of HCV reinfection

has decreased significantly from 2020 to 2023.¹²² Regular surveillance, timely diagnosis, and linkage to effective DAA treatment among at-risk populations are key to achieving micro-elimination of HCV in Taiwan.^{123,124}

To achieve holistic care beyond viral suppression, other important yet commonly overlooked issues, including bone health, malignancy, renal diseases, sexual health, vaccination, mental health, cognitive function decline, stigmatization, substance use, quality of life (QoL), and long-term care, should be evaluated and managed in routine HIV care. Comprehensive review for all comorbidities and their management in Taiwan is beyond the scope of this review. Selected topics of malignancy, mental health, cognitive function decline, and QoL will be briefly discussed.

The incidences of both AIDS-defining and non-AIDS-defining malignancies have decreased significantly in the era of combination ART.¹²⁵ However, the overall risk for malignancy remains higher among PWH compared to people without HIV. In one study analyzing data from NHIRD, the highest standardized incidence ratio was present in anal cancer in both sexes.¹²⁶ In a cross-sectional, single-center study, only 46.9 % of eligible PWH had completed free-of-charge cancer screening,¹²⁷ highlighting that awareness and implementation of screening for malignancy among PWH should be promoted.

Mental disturbances, including insomnia, anxiety, and depression, are common among Taiwanese PWH. In one study, over 30% of the participants receiving stable ART reported cognitive and psychological symptoms.¹²⁸ An NHIRD-based study showed that 23.8% of newly diagnosed PWH were diagnosed with psychiatric disorders after an average of 3.3 years of HIV diagnosis.¹²⁹ In another NHIRD study, PWH had a higher risk of any use and long-term use of benzodiazepines and Z-drugs compared with HIV-negative controls.¹³⁰

The prevalence of cognitive decline was 2.25 % among PWH with an average age of 37.5 years in a cross-sectional study.¹³¹ An older age, being less educated, and having a longer duration of HIV infection were significantly associated with cognitive impairment.¹³¹ Another study utilizing NHIRD found an incidence of 13.67 per 1000 person-years for neurological disorders.¹³² The associated factors identified included age, substance use, traumatic brain injury, psychiatric illness, HIV-associated opportunistic infections, frequency of emergency department visits, ART adherence, urbanization, and monthly income.

WHO has added a “fourth 90” aiming at optimizing health-related QoL (HRQoL) to the goal of HIV care. Research on QoL among PWH remains scarce in Taiwan. In a recent online survey of 120 virally suppressed PWH, similar HRQoL could be achieved compared to people without HIV across different dimensions including mobility, usual activities, self-care, pain/discomfort, and anxiety/depression.¹³³ The finding is encouraging, yet probably not generalizable to Taiwanese PWH who are female, older, less supported by CBOs, or living in rural areas. Patient-centered, holistic care covering aspects mentioned above will be needed to achieve the ambitious target of the fourth “90” for all PWH.

8. Conclusions

Taiwan is on the right track to achieve elimination of HIV infection as a public health threat by continued efforts and investment in expanding HIV testing and PrEP and providing free-of-charge, state-of-the-art antiretroviral regimens. Client-centered approaches are warranted to further scale up HIV testing. With continued progress of linkage to HIV treatment, more emphasis on the retention in treatment and prevention is needed to sustain the achievement. Delivery of information, education, and communication is imperative to reduce the stigma and discrimination surrounding HIV infection and to facilitate public-private partnership to ensure successful implementation of HIV control programs. While PWH continue to experience ongoing challenges of various comorbidities such as metabolic complications, sexually transmitted infections, malignancy, and mental disorders in the

modern ART era, holistic HIV care requires regular surveillance and evaluation of comorbidities with individualized preventive measurements to enhance the quality of life for PWH beyond viral suppression.

CRediT authorship contribution statement

Sung-Hsi Huang: Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation. **Hsun-Yin Huang:** Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation. **Stephane Wen-Wei Ku:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation. **Po-Hsien Kuo:** Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation. **Kuan-Yin Lin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation. **Guan-Jhou Chen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation. **Chia-Chi Lee:** Writing – review & editing, Validation, Formal analysis, Data curation. **Yen-Fang Huang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Conceptualization. **Chien-Ching Hung:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jmii.2024.11.003>.

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