

Policy recommendations for ending the HIV epidemic by 2030

March 31st, 2024

The project for establishment of the “bench-to-bedside” feedback system for sustainable ART and prevention of new HIV transmission in Vietnam



This policy recommendation involved the project members who participated in activities contributing to Output 1: “An effective ART monitoring system is established at target health facilities in Northern Vietnam,” and Output 2: “Causes of PrEP failure are analyzed” in SATREPS project for “Establishment of the ‘bench-to-bedside’ feedback system for sustainable ART and prevention of new HIV transmission” (implementation period: April 3, 2019, to April 2, 2024). These project members established a policy recommendation formulation subcommittee and deliberated the policy recommendation.

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Executive summary

In Vietnam, international support programs for HIV treatment are decreasing, and funding for HIV treatment is shifting to social insurance. This institutional change is accompanied by patients becoming responsible for medical fees and being transferred from urban areas to rural areas. As a result, there have been concerns that such changes will lead to a decline in treatment adherence, an increase in the number of cases of treatment failure due to inadequate treatment, an increase in the prevalence of drug-resistant viruses, and an increase in the spreading of drug-resistant viruses to newly infected patients. Additionally, in 2017, a program for providing pre-exposure prophylaxis (PrEP) to high-risk populations was introduced. PrEP uses the same drugs as those used in HIV treatment, so there have been concerns that the effects of PrEP programs would be limited by the onset, transmission, and spreading of drug-resistant viral infections due to the failure of antiretroviral therapy (ART).

Given this context, the following three activities were conducted as part of this project.

- 1. Virological monitoring of people living with HIV on ART and monitoring of the frequency of transmitted drug resistance in newly infected individuals**
- 2. Monitoring of HIV prevalence and drug resistance frequency in PrEP users**
- 3. Development of a monitoring system to promote the clinical use of test results**

The project will recommend the following policies based on the monitoring results to achieve Vietnam's national strategy.

Recommendation (1): Promote the dissemination and a stable supply of dolutegravir (DTG). Ensure annual virological monitoring and eliminate interfacility disparities in HIV treatment and care.

- Flexible institutional reform for achieving seamless HIV treatment and care
- Continuation of measures for keeping out-of-pocket costs for treatment low
- Further dissemination of DTG, early resolution of out-of-stock problems for DTG, and a stable supply of DTG
- Utilization of the urine β 2-microglobulin test and an early detection of renal dysfunction in tenofovir disoproxil fumarate (TDF) users
- Switching from TDF to tenofovir alafenamide (TAF) in patients with renal dysfunction

- Reducing disparities in the quality of HIV treatment and care between hospital levels
- Annual HIV viral load measurements and ensuring drug resistance testing in the event of treatment failure for non-nucleoside reverse transcriptase inhibitor (NNRTI) users

Recommendation (2): Improve service engagement and medication adherence among PrEP users and promote the expansion of effective PrEP.

- Improve service engagement and medication adherence for PrEP users
- Strengthen educational programs that promote the understanding of and autonomy for PrEP
- Collaborate with community organizations that are key players in HIV prevention
- Eliminate disparities in counseling skills among PrEP service providers
- Disseminate and thoroughly enforce existing PrEP initiation standard counseling procedures
- Implement drug resistance testing for people infected with HIV during PrEP use
- Strengthen collaboration among facilities that provide PrEP and continuously monitor PrEP users

Recommendation (3): Integrate and strengthen HIV informational systems

- Integrate HIV-related data systems into H-MED
- Develop informational systems that can track the cascade from prevention to treatment
- Develop an informational system for clinical patient management purposes (bench-to-bedside system)

Foreword

The SATREPS project for “Establishment of the ‘bench-to-bedside’ feedback system for sustainable ART and prevention of new HIV transmission in Vietnam” (SATREPS project) is being implemented under an agreement of the governments of Japan and Vietnam under the Record of Discussion, dated November 1, 2018, and the Ministry of Health of Vietnam Decision No. 5046, dated October 28, 2019. The fourth indicator for measuring this project’s goal is a “Final report including policy recommendation is submitted to Ministry of Health.” This policy recommendation was prepared by the project members as the final report and will be submitted to the Ministry of Health of Vietnam.

Background

Dramatic advances in therapeutic drugs have changed HIV infection from an incurable disease to a controllable disease, and reports indicate that the life expectancy of people living with HIV is almost the same as that of the general population if early detection and treatment are conducted. The UNAIDS “Global AIDS Strategy 2021–2026”¹ aimed to achieve “95-95-95”; that is, a 95% diagnosis rate, 95% treatment rate, and 95% viral suppression achievement rate, by 2025 (HIV care cascade), and this initiative announced the goal of ultimately ending the HIV epidemic by 2030. Furthermore, not only the diagnosis and treatment of people living with HIV but also the prevention of HIV infection are important for ending the HIV epidemic. The HIV care cascade needs to be enhanced, including the provision of preventive measures and education on multiple preventive measures, such as “U=U” (Undetectable=Untransmittable), condom use, and pre-exposure prophylaxis (PrEP). Consistent with this, the National Strategy to End the AIDS Epidemic by 2030 formulated by the government of Vietnam² also sets goals, such as communication for prevention awareness, expansion of prevention service coverage, expansion of HIV testing using various methods, and expansion and quality improvement of HIV treatment coverage.

National Strategy to End the AIDS Epidemic by 2030

General objective:

Strengthening HIV/AIDS prevention and control activities to reduce the number of new HIV infections and AIDS-related deaths, ending the AIDS epidemic in Vietnam by 2030, and minimizing the consequences of HIV/AIDS on socioeconomic development.

Specific objectives:

- (1) Scaling up and innovating communication activities, harm reduction interventions, and prevention, achieving 80% of people at high-risk accessing HIV prevention services by 2030.
- (2) Scaling up and diversifying forms of HIV testing and counseling, promoting community-based HIV testing services and HIV self-testing; achieving 95% of individuals living with HIV in the community knowing their HIV status by 2030; closely monitoring developments in the HIV/AIDS epidemic among high-risk groups.
- (3) Scaling up and improving the quality of HIV/AIDS treatment, achieving 95% of individuals living with HIV who know their status undergoing antiretroviral therapy (ART), achieving 95% of people on ART with viral suppression; and ending mother-to-child transmission of HIV by 2030.
- (4) Reinforcing and strengthening the capacity of the HIV/AIDS prevention and control system at all levels; ensuring human resources for HIV/AIDS prevention and control; and ensuring sustainable financing for HIV/AIDS prevention and control.

To date, Vietnam has continued to make progress in ending the HIV epidemic in accordance with its national strategy. However, with its recognition as a middle-income country due to economic growth, Vietnam has experienced a decrease in the number of international support programs for HIV treatment, such as testing and antiretrovirals. Since 2016, the government of Vietnam has shifted funding for HIV treatment from international aid programs to social health insurance and has continued to make efforts to maintain the principle of universal health coverage (UHC). This project was implemented amid this structural fiscal reform. In the provision of HIV treatment funded by social health insurance, patients are responsible for medical expenses, and as a general rule, they must go to medical facilities in their areas of residence in which they have registered their insurance card, leading to the possibility that they could be forced to transfer from urban areas to rural areas.

The treatment success rate³ and treatment retention rate⁴ at national hospitals, which have played a central role in HIV treatment in Vietnam for many years, are comparable to those in developed countries. However, there have been concerns that this institutional change may lead to a decline in treatment adherence, an increase in cases of treatment failure due to inadequate treatment, an increase in drug-resistant viruses, and an increase in the transmission of drug-resistant viruses in newly infected individuals.

Given this context, this project conducted activities focused on the following three points.

- 1. Virological monitoring of people living with HIV on antiretroviral therapy (ART) and**

monitoring of the frequency of transmitted drug resistance in newly infected individuals

We established a cohort of individuals infected with HIV receiving ART at a national hospital (National Hospital for Tropical Diseases) and 10 provincial- and district-level hospitals in North Vietnam, and we monitored the HIV viral load every 6 months. Drug resistance tests were conducted in cases in which the HIV viral load was ≥ 1000 copies/mL. We also conducted HIV viral load measurements and drug resistance tests for individuals newly infected with HIV at 10 provincial- and district-level hospitals.

2. Monitoring of HIV prevalence and drug resistance frequency in PrEP users

We used a PrEP cohort at Hanoi Medical University to monitor newly HIV-infected individuals after starting PrEP and conducted drug resistance tests in newly HIV-infected individuals during using PrEP.

3. Developing a monitoring system to promote the clinical use of test results

We developed a system that stores the HIV viral load and drug resistance test results measured in above-mentioned Item 1 and that enables for continuous data monitoring and rapid data feedback to clinical sites.

Project results and future issues

1. Virological monitoring of people living with HIV on ART and monitoring of the frequency of transmissible drug resistance in newly infected individuals

Maintaining favorable treatment outcomes

From 2019 to 2021, a cohort of 2,233 people living with HIV receiving ART was established, and they were continuously monitored for the HIV viral load and drug resistance until September 2023.

Progress was made in the transition of HIV treatment to social health insurance, and despite the impact of the novel coronavirus disease 2019 (COVID-19) pandemic from 2020–2021, a viral suppression rate of more than 90% (HIV viral load < 50 copies) was maintained during the observation period, and only 32 out of 2,233 individuals (1.4%) exhibited some kind of drug resistance mutation (as of August 2023). Furthermore, regarding the transmitted drug resistance (TDR), 601 newly infected individuals were registered in the project from December 2019 to March 2023 and underwent drug resistance testing before starting ART. The percentage of newly infected individuals with TDR was 5.9% in 2019–2020, 4.8% in 2021,

5.6% in 2022, and 3.9% in 2023, with the rate suppressed to a level similar to that of the national surveillance results conducted from 2017–2018 (5.8%)^{5,6}. The most common TDR mutations were related to non-nucleoside reverse transcriptase inhibitors (NNRTIs), and there were no mutations in integrase inhibitors observed.

Shifting HIV treatment to social health insurance

The shift of HIV treatment to social health insurance has not been progressing as rapidly as initially expected. That was one reason why favorable treatment outcomes were maintained, and the incidence and transmission of drug-resistant HIV did not increase. Measures have been taken with regards to the out-of-pocket costs of treatment fees by eliminating the obligation of the poor to pay out-of-pocket fees and having provincial People's Committees to cover out-of-pocket costs. Currently, ART is available free of cost at all of the 11 hospitals registered to participate in the project. Additionally, subsequent legal amendments to the general rule that patients must be transferred to the local hospital where their insurance card is registered (mainly district- or commune-level hospitals) to continue ART has resulted in the liberalization of access to provincial-level hospitals. It is thought that these flexible and gradual institutional reforms that are tailored to the actual circumstances in Vietnam have prevented an increase in cases of treatment failure, as well as the occurrence and spread of drug-resistant viruses, as we had concerned.

Introduction of dolutegravir (DTG)

Meanwhile, an integrase inhibitor, DTG, was newly introduced in Vietnam in 2017 following its recommendation by the WHO. The 2021 Ministry of Health of Vietnam HIV Treatment Guidelines (5968/QD-BYT) recommend switching to ART regimens that contain DTG in patients aged 10 years or older, and DTG has progressively seen a more widespread use. During the project period, 1,891 patients receiving ART switched to regimens containing DTG, and the incidences of viral loads of ≥ 200 copies and ≥ 1000 copies following DTG administration were low, at 2.82/100 person-years and 1.09/100 person-years, respectively, thereby confirming the viral suppression effect of DTG (as of August 2023). Additionally, no cases of drug resistance to DTG have been observed in on-ART patients. The expansion of DTG, which has a high viral suppression effect and high genetic barrier against drug resistance, will further improve HIV treatment outcomes in Vietnam, and it can be said that is a major step toward the national strategic goal of eradicating AIDS by 2030.

However, the expanded use of DTG is not necessarily progressing uniformly across all regions or facility levels. Variation in DTG prescription statuses was demonstrated among the

11 hospitals registered in the project (percentage of patients using DTG: 1.0–98.4%). Furthermore, of the 1,891 patients who changed to regimens containing DTG during the project period, 292 (15.4%) experienced DTG discontinuation, with the most common reason for discontinuation was DTG stockout (236 patients, 80.8%). Furthermore, one hospital that discontinued DTG due to stockout subsequently exhibited a spike in cases, with viral loads increasing to more than 200 copies. These results suggest that the stable procurement of DTG is an urgent issue for maintaining viral suppression. Furthermore, DTG is often used as a combination of tenofovir disoproxil fumarate (TDF)/lamivudine (3TC)/DTG, and among the reasons for DTG discontinuation, renal dysfunction was the second-most common reason, following stockout. The impact of TDF on the kidney may be greater in the Vietnamese population than other populations, as Vietnamese individuals have a lower body weight compared to Westerners^{7,8}. Results confirmed that the monitoring for renal dysfunction is important when using a TDF/3TC/DTG combination drug.

As mentioned above, Vietnam has maintained favorable HIV treatment outcomes as the shift of HIV treatment to social health insurance progresses, thanks in part to the expanded use of DTG, which has a high viral suppression effect. A stable DTG supply and further expansion of DTG are expected in the future.

Disparities in HIV treatment and care among hospital levels

Meanwhile, the project also confirmed cases with intermittently high viral loads. Compared with national-level hospitals, lower-level hospitals (i.e., provincial level or district level) were associated with higher treatment failure rates (viral loads of ≥ 200 copies or ≥ 1000 copies). Disparities among hospital levels may also exist in terms of the quality of HIV treatment and care, such as an effective adherence support and the selection of ART regimens based on the HIV viral load and drug resistance test results. Continuous monitoring of the HIV viral load and drug-resistant viruses is particularly necessary in lower-level facilities where less progress has been made in the stable procurement and use of DTG, and comprehensive adherence support and effective ART management skills need to be improved. At the end of June 2023, the free supply of antiretroviral drugs from the United States President's Emergency Plan for AIDS Relief (PEPFAR) to the National Hospital for Tropical Diseases (NHTD) came to an end, and NHTD patients also began to receive ART using social health insurance. This has resulted in increased transfers to provincial- and district-level hospitals. Addressing disparities in care between hospital levels is important for maintaining favorable treatment outcomes.

Furthermore, drug resistance results for patients who failed treatment demonstrated that

approximately 30% had no drug resistance or were able to continue the first-line treatment despite drug resistance. Adherence support is particularly important in such cases. However, barriers to adherence and effective ART management are not limited to just the individual patient and family. A variety of factors are in play, including hospital-related factors, such as insufficient medical skills, insufficient human resources, and insufficient collaboration among medical teams, as well as factors related to the medical system, discrimination and prejudice, and society. Therefore, this project focused on hospital-level factors, and training workshops for health care workers were held from 2022 to 2023, with this information being compiled into a reference book (HIV Drug Resistance Knowledge Book). These activities were conducted together with the Vietnam Administration of HIV/AIDS Control (VAAC) of the Ministry of Health of Vietnam and Vietnamese HIV experts.

Barriers to virological monitoring

We also witnessed and heard about issues related to virological monitoring during the project activities. First, the 2021 HIV Treatment Guidelines (5968/QD-BYT) stipulated that HIV viral load tests should be conducted at 6 months and 12 months after starting ART and every 12 months afterwards, but viral load tests according to the guidelines have not been provided to all patients. Drug resistance tests are also recommended in patients exposed to multiple ART regimens before switching to a second- or third-line regimen, but drug resistance tests are rarely conducted for clinical purposes. This is because drug resistance tests are not covered by social health insurance, so the entire cost of the tests must be borne by the individual and because the number of facilities that can perform HIV viral load and drug resistance tests in Vietnam is limited. HIV viral load tests are mainly conducted at hospitals at the provincial level and higher, but even hospitals with measuring equipment may, at times, not utilize such equipment in an effective manner due to the lack of financial resources for purchasing reagents. Drug resistance tests are rarely conducted at institutions other than the two research institutions conducting drug-resistant HIV surveillance (National Institute of Hygiene and Epidemiology, NIHE; and Pasteur Institute of Ho Chi Minh City, PI HCMC). Test can be requested to another facility if performing viral load tests are not possible at the individual's facility, but the cost of transporting specimens is not covered by social health insurance. Furthermore, tests sometimes cannot be conducted due to delays in reimbursement of test costs from Vietnam Social Security (VSS). These structural factors act as barriers to the continued monitoring of HIV viral load and drug-resistant viruses.

Summary of issues and results

Result	Issue
<ul style="list-style-type: none"> ● During the period of shifting HIV treatment to social health insurance, the viral load was maintained at a low level from 2019 to 2023, and the incidence of drug resistance was also low. ● From 2019 to 2023, the transmission of drug-resistant HIV to newly infected individuals was suppressed to a low level. ● DTG use has progressively expanded, and the high viral suppression effect of DTG and the genetic barrier to drug resistance have been demonstrated. 	<ul style="list-style-type: none"> ● Some facilities have restrictions on the use and stable procurement of DTG, which is a factor contributing to treatment failure. ● Monitoring for renal dysfunction is important when using a combination drug of TDF/3TC/DTG. ● Disparities in HIV treatment and care skills between facilities are a factor in treatment failure. ● Structural factors, such as there being an insufficient number of testing facilities, an insufficient financial resources for reagent purchase and sample transportation costs, and an immature social health insurance system, are barriers to virological monitoring.

2. Monitoring of HIV prevalence and drug resistance frequency in PrEP users

Monitoring of new HIV infections after PrEP has been performed among 4,254 participants of the Hanoi Medical University PrEP cohort (HMU-PrEP). From May 2019 to March 31, 2023, 3,111 participants received two or more HIV tests, and during the observation period (total observed person-years: 3,408 person-years), 31 participants were newly infected with HIV, with an HIV incidence of 0.91/100 person-years. HIV incidence among PrEP users vary by country, region, and program⁹⁻¹⁵, but the HIV incidence in Vietnam HMU-PrEP cannot confirmed to be low when considering that taking PrEP as prescribed reduces the risk of sexually transmitted HIV infection by approximately 99%.

Of the 31 people infected with HIV during the observation period, 7 (22.6%) were demonstrated to have been infected within 90 days after starting PrEP, suggesting that they may have already been infected with HIV when starting PrEP (i.e., initial test was a false negative). Additionally, 22 people underwent drug resistance tests, of which 5 (22.7%) exhibited some kind of drug resistance mutation. M184V, which is highly resistant to the drug used in PrEP (3TC), was confirmed in two participants (9.1%). These two participants were

infected with HIV 36 days and 83 days after starting PrEP, respectively, and it is not possible to determine whether they acquired HIV resistance due to taking PrEP or were infected by a resistant strain (TDR).

Meanwhile, with HMU-PrEP, the retention rate 12 months after starting PrEP decreased to approximately 40%, and of the 31 participants who were demonstrated to be infected with HIV, 15 (48.4%) did not undergo examinations a single time since starting PrEP until they were demonstrated to have been infected with HIV. The prescription history suggested that, of the 31 participants, 23 (74.2%) had used up their prescription drugs before they were demonstrated to have been infected with HIV, and the blood concentrations of the drugs used for PrEP (TDF and 3TC) were also low in most cases. These results suggest that HIV infection while using PrEP is more likely due to the initial HIV infection being overlooked at the initiation of PrEP and discontinuation of drug medication or poor drug adherence after starting PrEP rather than infection due to the transmission of drug-resistant viruses. The HIV incidence after PrEP enrollment may further increase when including unreported cases of HIV infection after withdrawal from the PrEP program. Screening for acute HIV infection and effective adherence counseling when starting PrEP are needed.

Furthermore, HMU-PrEP exhibited differences in subsequent withdrawal rates depending on the PrEP program’s recruitment method. Those who started PrEP through mobile clinics, community-based organizations (CBOs), and outreach efforts had a lower PrEP withdrawal rate than those who started PrEP due to referrals from clinics or other PrEP users. The correct understanding of PrEP, as well as motivation and autonomy when starting PrEP, may have also influenced the subsequent PrEP continuation. Efforts are also needed to eliminate disparities in counseling skills among PrEP service providers.

Since its launch in 2017, PrEP in Vietnam has expanded to more than 200 facilities in 29 provinces, and by 2022, more than 60,000 people have undergone PrEP. However, information sharing between facilities that provide PrEP is insufficient, and individuals who withdrew from HMU-PrEP may have continued PrEP at other facilities. Verifying the effectiveness and retention rate of PrEP and maximizing its effects requires strengthening the collaboration among facilities that provide PrEP and continuously monitoring PrEP users.

Summary of issues and results

Result	Issue
<ul style="list-style-type: none"> ● HIV incidence during PrEP use is not low (0.91/100 person-years). ● HIV infection while using PrEP is often 	<ul style="list-style-type: none"> ● Screening for acute HIV infection and effective adherence counseling when starting PrEP are insufficient.

<p>due to overlooked initial HIV infection at the start of PrEP and discontinuation of drug medication or poor drug adherence after starting PrEP.</p>	<ul style="list-style-type: none"> ● Disparities in counseling skills among PrEP service providers influence PrEP withdrawal rates. ● There is no sufficient collaboration among facilities that provide PrEP, and continuous monitoring after starting PrEP is not possible.
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3. Developing a monitoring system to promote the clinical use of test results

In this project, we built a cloud network system called the HIV Data Network system (HDN) that connects NHTD with 10 hospitals in North Vietnam. HDN is a system that demonstrates the status of sample transportation, test implementation, and results, and viral load test results that are entered by laboratories are shared with clinical sites in a timely manner. The system displays not only a list of viral loads from past to present but also the history of antiviral drug (ARV) use, which is useful for patient management. HDN also has a function of collecting data on drug resistance. When a testing institution enters sequence data, HDN accesses the Stanford University HIV Drug Resistance Database (<https://hivdb.stanford.edu/>) and automatically displays drug resistance test results. As with viral load measurements, results can be shared in a timely manner, and testing institutions can save time in creating result slips. Such functions were highly praised by Vietnamese health care workers as being useful for the rapid return of test results and patient management in clinical settings.

VAAC has developed H-MED, which is a system aimed at managing HIV/AIDS control programs and is being operated in ART outpatient clinics nationwide. In the future, Vietnam's HIV data system will be integrated into H-MED. H-MED has the ability to collect various data, such as ARV inventory management, ART use history, viral load, tuberculosis, hepatitis, and PrEP, but it does not have the ability to collect data on drug resistance tests, and it only has surveillance information. Therefore, the project integrated HDN's drug resistance testing functions into H-MED. This enabled drug resistance test results to be viewed at each hospital using H-MED, and VAAC is now able to accumulate data on drug resistance testing conducted in clinical settings. The project's HIV sequence data was also able to be transferred to VAAC.

However, issues remain with the data systems used in ART outpatient clinics. First, multiple data systems are being used. There is not only H-MED but also those developed by VAAC, such as HIV info 4.0 and PDMA; those developed by each project, such as HDN; and those necessary for medical expense settlement using social health insurance. Information

about patients' needs to be entered into multiple systems. This not only places a large burden on health care workers but also requires the referencing of multiple systems, such as referencing H-MED for HIV viral load tests and other systems for other tests or items. Next, the PrEP, HIV test, and ART systems are not linked, so following the cascade from prevention to treatment in a single system is not possible. Furthermore, the purpose of the system is limited to national HIV/AIDS control program management, such as reporting aggregate data (reporting WHO indicator data). It is difficult to utilize the data for clinical patient management. For example, past test results are not displayed as a list, which makes it difficult to follow a patient's progress.

Summary of issues and results

Result	Issue
<ul style="list-style-type: none"> ● HDN was highly praised as being useful for the rapid return of test results and patient management in clinical settings. ● HDN's drug resistance data collection function has been integrated into H-MED, which made it possible to share results in a timely manner and accumulate data on drug resistance tests conducted in clinical settings, which are features of HDN. 	<ul style="list-style-type: none"> ● Multiple data systems are used in ART outpatient clinics, so there is a large burden imposed on health care workers involved in data entry. ● The PrEP, HIV test, and ART systems are not linked, so following the cascade from prevention to treatment in a single system is not possible. ● The purpose of use of the system is limited to national HIV/AIDS control program management, and the data entered into the system cannot be used for clinical patient management.

Policy recommendations

Recommendation (1): Promote the dissemination and a stable supply of DTG. Ensure annual virological monitoring and eliminate interfacility disparities in HIV treatment and care.

The project results demonstrated that the flexible and gradual financial reform of HIV treatment by the government of Vietnam prevented the increase in treatment failure cases as well as the emergence and spread of drug-resistant viruses, which we had concerned, and contributed to the maintenance of effective treatment. The biggest concerns of people living with HIV about shifting to social health insurance financing for HIV treatment are whether

they can continue attending familiar hospitals, whether they can receive high-quality HIV treatment and care, and whether their HIV status will not be known to local residents¹⁶. It is the hope that flexible institutional reforms will continue to be implemented in order to address the concerns and anxieties of people living with HIV and to achieve seamless HIV treatment and care. In particular, continuing measures to keep out-of-pocket payments for treatment at a low level will help maintain the viral suppression rate.

This project has demonstrated a high viral suppression effect of DTG and the genetic barrier to drug resistance. Further dissemination and a stable supply of DTG in Vietnam will be an important aspect of achieving the national strategy. Factors that impede achieving a stable supply of DTG, such as the insufficient roles and collaboration of each institution involved in its procurement and the lack of development of laws and guidelines, need to be identified, and problems of the drug stock-out need to be resolved as soon as possible. Additionally, the risk of renal dysfunction increases when using a combination drug of TDF/3TC/DTG. Prior to this project, the National Center for Global Health and Medicine conducted joint research with NHTD and confirmed the utility of urinary beta-2 microglobulin (β 2MG) as a marker for the detection of renal tubular damage, which is a precursor to renal dysfunction⁷. Monitoring of urinary β 2MG in TDF users is recommended as a marker for the early detection of renal dysfunction. Switching from TDF to tenofovir alafenamide (TAF) is recommended for patients with renal dysfunction.

Furthermore, annual HIV viral load measurements prescribed by current treatment guidelines should continue until DTG becomes widespread and stable. In particular, for patients using NNRTIs as a key drug, drug resistance tests are also recommended in the event of treatment failure so that appropriate ART drugs can be selected and adherence support can be implemented at the appropriate time. The dissemination of drug resistance tests in clinical settings, as well as the conditions for drug resistance tests to be covered by social health insurance, should also be reconsidered. Additionally, further studies and appropriate responses are required to address the structural factors that impede virological monitoring that were observed in this project.

Virological monitoring has clinical significance only when the monitoring results are appropriately interpreted and applied to treatment and care. In particular, the most important key to HIV treatment is medication adherence. Continued efforts need to be made to narrow disparities between hospital levels in terms of the quality of HIV treatment and care, such as effective adherence support and the selection of ART regimens. It is the hope that the HIV Drug Resistance Knowledge Book developed in this project will be disseminated and utilized nationwide.

This recommendation contributes to the achieving of national strategy objectives (3) and (4).

Recommendation (2): Improve service engagement and medication adherence among PrEP users and promote the effective expansion of PrEP.

The information obtained through this project suggests that the HIV incidence while using PrEP is not necessarily low, and the biggest causes of HIV infection were demonstrated to be overlooked by initial HIV infection at the start of PrEP and discontinuation of drug medication or poor drug adherence after starting PrEP. Over 5 years since the start of the PrEP program, Vietnam should move beyond improving access to PrEP services and aim to expand “effective PrEP services” with a focus on maximizing PrEP preventive effects.

The effectiveness of PrEP is ensured by taking the medication as prescribed, and engagement with PrEP services is key to PrEP success. Decisions such as whether to start PrEP, whether to continue medication, administration methods, risky behaviors during medication, and relationships with partners are left to the PrEP users, and various determinations must be made by themselves. Continuous implementation of educational programs that promote the understanding and autonomy of PrEP is required, such as correctly understanding PrEP and appropriately evaluating one’s own HIV prevention needs, deciding on the necessity for PrEP and administration methods based on their own needs, and developing living environments and interpersonal relationships that enable PrEP administration^{17,18}. There are particularly high expectations for collaborations with community-based organizations (CBOs), which are key players involved in HIV prevention in Vietnam.

HMU-PrEP also exhibited differences in subsequent withdrawal rates depending on the PrEP program recruitment method. Factors that impede the continuation of PrEP (socioeconomic circumstances, side effects, or stigma) vary among users¹⁹⁻²¹. Disparities in counseling skills among PrEP service providers need to be eliminated, and support needs to be given for the continuation of PrEP using a holistic approach that responds to individual needs. It is important to disseminate and thoroughly enforce the existing standard procedures for counseling at the start of PrEP. Improving engagement with PrEP services will also lead to the early detection and early treatment of HIV infection.

Of the 22 individuals in HMU-PrEP who became infected with HIV after starting PrEP and who underwent drug resistance tests, 5 exhibited some kind of drug resistance mutation, and 2 exhibited a PrEP-associated drug resistance mutation (M184V). Determining whether these two people acquired HIV resistance through PrEP use or were infected with a resistant

stain was difficult, and further evaluation and study will be necessary in the future. Recently published data on new HIV infections in the United States demonstrated a strong association between the history of PrEP use and presence of M184I/V²². The rapid expansion of PrEP in Vietnam and the poor medication adherence observed with HMU-PrEP suggests that conducting drug resistance tests as recommended by the WHO is desirable for people infected with HIV during PrEP use²³. Drug resistance tests not only enable the selection of appropriate first-line treatment drugs but also evaluate the impact of drug-resistant HIV on the effectiveness of PrEP.

Although PrEP is rapidly expanding in Vietnam, collaboration among facilities that provide PrEP remains insufficient. H-MED, which was developed by VAAC for the purpose of HIV/AIDS control program management, allows for the management of PrEP-related information. However, H-MED is not used by all facilities that provide PrEP, and only information on their own PrEP users can be viewed and edited. Therefore, if a PrEP user enrolls in a PrEP program or starts ART at another facility, then this information will not be visible in the system. Given the current status of a large number of people withdrawing from PrEP programs, there is a need for strengthening collaboration among facilities and ensuring that PrEP users are continuously monitored even after they withdraw from one program.

This recommendation contributes to the achieving of national strategy objectives (1) and (4).

Recommendation (3): Integrate and strengthen HIV informational systems

HIV data systems should be integrated into H-MED and unified as determined by VAAC to avoid duplication of collected data and reduce the burden of data entry by health care workers. We also recommend the development of a system that integrates PrEP, HIV testing, and ART data systems, and which can track the cascade from prevention to treatment. The WHO recommends the use of cascade data for identifying and appropriately linking gaps in HIV care²⁴. Furthermore, we propose the development of not only a system for program management such as collection of aggregated data, but also a system for clinical patient management (bench-to-bedside system). Systems for patient management can improve the quality of health care services by supporting health care workers and facilitating the clinical use of data²⁵. We propose the discussion of making H-MED a system that can also be used for patient management in the future, or developing a separate system for patient management, as well as formulating a plan for strengthening the health informational system. Interoperable program management systems and patient management systems are desirable. This reduces the burden of data entry on health care workers and enables the accumulation of data that

reflects clinical practice^{26,27}.

This recommendation contributes to the achieving of national strategy objective (4).

References:

- 1 UNAIDS. Global AIDS Strategy 2021–2026-End Inequalities. End AIDS. (2021).
- 2 Government of Vietnam. National Strategy to End the AIDS Epidemic by 2030. (2020).
- 3 Tanuma, J. et al. Long-term viral suppression and immune recovery during first-line antiretroviral therapy: a study of an HIV-infected adult cohort in Hanoi, Vietnam. *Journal of the International AIDS Society* 20, doi:10.1002/jia2.25030 (2017).
- 4 Matsumoto, S. et al. High Treatment Retention Rate in HIV-Infected Patients Receiving Antiretroviral Therapy at Two Large HIV Clinics in Hanoi, Vietnam. *PLoS one* 10, e0139594, doi:10.1371/journal.pone.0139594 (2015).
- 5 Dat, V. Q. et al. The prevalence of pre-treatment and acquired HIV drug resistance in Vietnam: a nationally representative survey, 2017-2018. *Journal of the International AIDS Society* 25, e25857, doi:10.1002/jia2.25857 (2022).
- 6 Tanuma, J. et al. Low prevalence of transmitted drug resistance of HIV-1 during 2008-2012 antiretroviral therapy scaling up in Southern Vietnam. *Journal of acquired immune deficiency syndromes (1999)* 66, 358-364, doi:10.1097/qai.000000000000196 (2014).
- 7 Mizushima, D. et al. Tenofovir disoproxil fumarate co-administered with lopinavir/ritonavir is strongly associated with tubular damage and chronic kidney disease. *Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy* 24, 549-554, doi:10.1016/j.jiac.2018.03.002 (2018).
- 8 Mizushima, D. et al. Low body weight and tenofovir use are risk factors for renal dysfunction in Vietnamese HIV-infected patients. A prospective 18-month observation study. *Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy* 20, 784-788, doi:10.1016/j.jiac.2014.08.015 (2014).
- 9 Wahome, E. W. et al. PrEP uptake and adherence in relation to HIV-1 incidence among Kenyan men who have sex with men. *EClinicalMedicine* 26, 100541, doi:10.1016/j.eclinm.2020.100541 (2020).
- 10 Laurent, C. et al. Human Immunodeficiency Virus Seroconversion Among Men Who Have Sex With Men Who Use Event-Driven or Daily Oral Pre-Exposure Prophylaxis (CohMSM-PrEP): A Multi-Country Demonstration Study From West Africa. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 77, 606-614, doi:10.1093/cid/ciad221 (2023).
- 11 Grant, R. M. et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *The Lancet. Infectious diseases* 14, 820-829, doi:10.1016/s1473-3099(14)70847-3 (2014).
- 12 Molina, J. M. et al. Daily and on-demand HIV pre-exposure prophylaxis with emtricitabine

- and tenofovir disoproxil (ANRS PREVENIR): a prospective observational cohort study. *The lancet. HIV* 9, e554-e562, doi:10.1016/s2352-3018(22)00133-3 (2022).
- 13 Koss, C. A. et al. HIV incidence after pre-exposure prophylaxis initiation among women and men at elevated HIV risk: A population-based study in rural Kenya and Uganda. *PLoS medicine* 18, e1003492, doi:10.1371/journal.pmed.1003492 (2021).
- 14 Grulich, A. E. et al. Long-term protection from HIV infection with oral HIV pre-exposure prophylaxis in gay and bisexual men: findings from the expanded and extended EPIC-NSW prospective implementation study. *The lancet. HIV* 8, e486-e494, doi:10.1016/s2352-3018(21)00074-6 (2021).
- 15 Vuylsteke, B. et al. Daily and event-driven pre-exposure prophylaxis for men who have sex with men in Belgium: results of a prospective cohort measuring adherence, sexual behaviour and STI incidence. *Journal of the International AIDS Society* 22, e25407, doi:10.1002/jia2.25407 (2019).
- 16 Matsumoto, S. et al. The patient voice: a survey of worries and anxieties during health system transition in HIV services in Vietnam. *BMC international health and human rights* 20, 1, doi:10.1186/s12914-019-0221-7 (2020).
- 17 Zhai, Y., Isadore, K. M., Parker, L. & Sandberg, J. Responding to the HIV Health Literacy Needs of Clients in Substance Use Treatment: The Role of Universal PrEP Education in HIV Health and Prevention. *International journal of environmental research and public health* 20, doi:10.3390/ijerph20196893 (2023).
- 18 Toledo, L., McLellan-Lemal, E., Henderson, F. L. & Kebaabetswe, P. M. Knowledge, Attitudes, and Experiences of HIV Pre-Exposure Prophylaxis (PrEP) Trial Participants in Botswana. *World journal of AIDS* 5, 10-20, doi:10.4236/wja.2015.51002 (2015).
- 19 Kimani, M. et al. "I wish to remain HIV negative": Pre-exposure prophylaxis adherence and persistence in transgender women and men who have sex with men in coastal Kenya. *PLoS one* 16, e0244226, doi:10.1371/journal.pone.0244226 (2021).
- 20 MacDonald, J. et al. Improving HIV pre-exposure prophylaxis (PrEP) adherence and retention in care: Process evaluation and recommendation development from a nationally implemented PrEP programme. *PloS one* 18, e0292289, doi:10.1371/journal.pone.0292289 (2023).
- 21 Jalil, E. M. et al. Low PrEP adherence despite high retention among transgender women in Brazil: the PrEPParadas study. *Journal of the International AIDS Society* 25, e25896, doi:10.1002/jia2.25896 (2022).
- 22 Misra, K. et al. Pre-exposure prophylaxis (PrEP) use history in people with antiretroviral resistance at HIV diagnosis: Findings from New York City HIV surveillance and partner

- services, 2015-2022. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, doi:10.1093/cid/ciad699 (2023).
- 23 HIV drug resistance surveillance in countries scaling up pre-exposure prophylaxis. (2020).
- 24 World Health Organization. HIV strategic information for impact: cascade data use manual: to identify gaps in HIV and health services for programme improvement: user manual. (2018).
- 25 The office of the National Coordinator for Health Information Technology (ONC). Health IT and Health Information Exchange Basics. (2017).
- 26 Karunganwa, N. et al. Fostering interoperability for Data Exchange across Health Information Systems in Uganda. (2022).
- 27 Bigten R. et al. Integrating Electronic Medical Records Data into National Health Reporting System to Enhance Health Data Reporting and Use at the Facility Level. 15th International Conference on Social Implications of Computers in Developing Countries (ICT4D) (2019).