



HIV drug resistance in Southeast Asia: prevalence, determinants, and strategic management

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Background: Human immunodeficiency virus (HIV) drug resistance is the ability of HIV to mutate such that it reduces the ability of antiretroviral drugs to block virus replication. This can lead to suboptimal treatment outcomes, treatment failure and continued community transmission of drug resistant HIV strains. The rapidly rising HIV drug resistance rates in low- and middle-income countries pose a critical challenge to ending the HIV epidemic. In Southeast Asia, where national surveillance of HIV drug resistance is lacking, there is an urgent need to understand this public health issue to effectively curb HIV.

Methods: Literature review and interviews with key informants across Southeast Asia were conducted to understand the trends of HIV drug resistance in Southeast Asia, including prevalence rates, factors causing drug resistance, and policy strategies for combating HIV drug resistance.

Results: HIV drug resistance prevalence rates in Southeast Asia were generally low to moderate. The key determinants of HIV drug resistance identified relate to barriers undermining treatment adherence and retention, particularly geographical access and the cost of travelling for treatment, stigma and discrimination, and the lack of patient confidentiality at health facilities. Most Southeast Asian countries have adapted WHO treatment guidelines and were in the process of transiting to using antiretroviral drugs with higher genetic barriers to resistance. However, resource constraints and limited laboratory capacity have hindered their ability to conduct routine viral load monitoring for all patients and testing of HIV drug resistance.

Conclusions: Most Southeast Asian countries are making progress in managing HIV drug resistance. However, to achieve the UNAIDS global target of maximal viral load suppression in 90% of all people receiving antiretroviral therapy, Southeast Asian countries need to address barriers to treatment adherence and retention, expand viral load testing coverage and drug resistance testing availability, and make dolutegravir available as a treatment option.

Keywords: Human immunodeficiency virus (HIV); drug resistance; Southeast Asia

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Introduction

HIV drug resistance (HIVDR) refers to the process of HIV mutating to reduce the ability of antiretroviral drugs to block virus replication (1). HIVDR can lead to suboptimal treatment outcomes, treatment failure and continued community transmission of drug resistant HIV strains (2), posing a critical challenge to achieving the UNAIDS 90-90-90 target to end the AIDS (acquired immunodeficiency syndrome) epidemic, particularly the third 90 target of achieving viral suppression among 90% of people living with HIV who have initiated antiretroviral therapy (ART) (3).

Broadly, HIVDR may be divided into three categories (4). First, transmitted HIVDR (TDR) refers to HIVDR detected in people with no history of antiretroviral drug exposure. TDR occurs because these people have been infected by a HIV strain with drug-resistant mutations (4). Second, acquired HIVDR (ADR) refers to HIVDR emerging in people receiving ART. This is due to drug selection pressure (5). Antiretroviral drugs exert selection pressure by eliminating HIV strains which are not drug resistant. Drug-resistant strains which survive continue to replicate and adapt, eventually becoming the dominant HIV strain and leading to treatment failure as the patient has become resistant to the antiretroviral drug used (6). Several factors may exacerbate selection pressure, such as lapses in treatment adherence or non-optimal drug regimens (7). Third, pre-treatment HIVDR (PDR) refers to HIVDR detected in people initiating or re-initiating ART. PDR can result from TDR, ADR, or both. Individuals may have acquired PDR through transmission from others or prior exposure to ARV drugs (e.g., pre-exposure prophylaxis, antiretroviral drugs for prevention of mother-to-child transmission) (4).

Global trends in HIVDR prevalence

Globally, high income countries had higher incidence of HIVDR than low and middle-income countries (LMICs) (8,9). Median TDR prevalence rates between 2014–2019 were 8.5% in Europe, 14.2% in North America, and 8.7% in high-income countries in Asia (9). Despite the high prevalence rates, TDR was less of a concern in high-income countries because regular HIVDR testing is available to guide the selection of ART and there is a wide range of ART options available (10).

In contrast, HIVDR prevalence in LMICs was lower but on the rise (8-11). Across at-risk populations in LMICs, TDR prevalence almost doubled from 2004–2008 to 2009–

2013 [men who have sex with men (MSM): 4.2% *vs.* 7.8%; heterosexuals: 2.6% *vs.* 4.1%; intravenous drug users (IDU): 2.4% *vs.* 4.8% respectively] (10). Between 2009–2013 and 2014–2019, median TDR prevalence increased markedly from 3.6% to 6.0% in Sub-Saharan Africa, and trended upwards in South/Southeast Asia (3.3% to 4.15%) and Latin America/the Caribbean (9.35% to 9.4%) (9). Resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs has been particularly rampant in LMICs because of its low genetic barrier to resistance, and is a serious concern because NNRTIs have been widely used in first-line ART regimens across LMICs (12,13). Between 2014–2018, 12 out of 18 LMICs conducting HIVDR surveillance found NNRTI PDR in more than 10% of adults initiating ART in each country (4). The estimated prevalence of NNRTI PDR in 2016 was 11.0% in southern Africa, 10.1% in eastern Africa, 7.2% in western and central Africa, and 9.4% in Latin America and the Caribbean, and just 3.2% in Asia (11).

HIVDR prevalence in Southeast Asia

Several studies have examined the prevalence of HIVDR in selected Southeast Asian countries (4,5,8-10,14-16). In general, TDR prevalence was lower in Southeast Asia compared to other regions (5,8-10,14). Rhee *et al.* (9) found that South/Southeast Asia was the region with the lowest TDR prevalence rates. Another systematic review and meta-analysis focusing on at-risk populations similarly found that TDR prevalence were lower among at-risk populations in South/Southeast Asia compared to other regions (e.g., for MSM, 15.5% in Oceania, 13.7% in North America, 11.0% in Western Europe, 10.2% in Eastern Europe and Central Asia, 8.3% in South America, 7.8% in East Asia, and 2.8% in South/Southeast Asia) (10). However, these studies combined the South and Southeast Asia regions in their analysis.

Similarly, low rates of HIVDR have been reported in other studies examining South-East Asia Region based on the World Health Organization (WHO)'s classification. Trotter *et al.*'s (5) systematic review reported that most studies found low levels of HIVDR, but only data from Thailand and India were available, meaning that findings were not likely to be representative of the region. Finally, the 2021 WHO HIV Drug Resistance Report (14) noted that the prevalence of PDR in the WHO South-East Asia Region was in general lower than in other regions—for antiretroviral drugs efavirenz or nevirapine, PDR was 16.7% in the Americas, 15.4% in Africa, 6.9% in Western

Pacific, and 5.3% in South-East Asia. However, the WHO South-East Asia region includes some South Asian countries and does not include some Southeast Asian countries which are classified under the Western Pacific region (i.e., Brunei, Cambodia, Philippines, Singapore, Lao People's Democratic Republic (Lao PDR), Malaysia, Viet Nam).

To the best of the authors' knowledge, there has not been a comprehensive review of HIVDR prevalence across all countries in Southeast Asia (namely, Brunei, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, the Philippines, Singapore, Timor Leste, Thailand, and Viet Nam). This study therefore aims to conduct a review on the state-of-the-art of HIVDR by examining its prevalence, determinants and management in Southeast Asia.

Factors contributing to HIVDR

Factors contributing to HIVDR can be classified into four categories: programmatic factors, patient-related factors, regimen- and drug-related factors, and viral factors (17).

Programmatic factors

Programme-level factors such as resource limitations and poor health infrastructure contribute to HIVDR (17). Many health facilities in LMICs have struggled with delivering optimal care due to resource limitations (e.g., drug stock-outs, manpower shortages) (5,18). In health facilities which lack access to routine viral load monitoring and HIVDR testing, virological failure cannot be detected in a timely manner (5,19). Delayed treatment initiation, a flow-on effect of limited resources and poor healthcare infrastructure, is another programmatic factor contributing to HIVDR (20). Programme-level factors also hinder treatment adherence and patient retention. For example, long wait times at the clinic and lack of follow-up from hospital staff are known to discourage treatment adherence (21,22). Additionally, while increased access to ART through programmes such as universal ART for children has been vital for progress towards the 90-90-90 treatment cascade, it has contributed to the transmission and development of HIVDR in places where programme rollout has been suboptimal due to the abovementioned logistics and health system barriers (23,24).

Patient-related factors

Strict adherence to ART is vital for treating HIV effectively. Poor adherence to ART is known to increase the likelihood

of virological failure, emergence of HIVDR, worsening of the HIV infection, and death (25-34). One key reason for patients' poor adherence and retention is treatment fatigue. ART requires lifelong adherence to medication despite its adverse side effects. This involves significant adaptations to daily routines to fit medication regimens, follow up appointments, and prescription refills. High pill burden, frequent hospital visits, side effects, and dosing restrictions are reasons that lead to fatigue and non-adherence (35). Other psychological factors which may hinder adherence include mental health issues, drug abuse, cognitive decline, and absent-mindedness (36,37). Poverty, underdevelopment, and food insecurity are systemic issues which have impeded patient adherence (19,37-39). For example, patients may not be able to afford the cost and time taken to travel to the nearest clinic.

Regimen- and drug-related factors

HIVDR is most likely to emerge when the antiretroviral drugs used have a low genetic barrier to developing drug resistance. This includes many antiretroviral drugs previously recommended in the first-line treatment regimens, e.g., nucleoside reverse transcriptase inhibitors (NRTIs) such as abacavir, zidovudine, lamivudine and tenofovir, and non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as efavirenz and nevirapine (24,40). As such, the WHO has revised their treatment guidelines to recommend dolutegravir as the preferred HIV treatment option because of its high genetic barrier to resistance (41).

Suboptimal drug regimens also contribute to HIVDR, particularly among the paediatric population as limited ART options are available, making regimen modifications difficult. What is available may still be complex to administer or unpalatable to children (20,42-44). Finally, interactions between drugs can reduce the concentration of ARV drugs to suboptimal levels (17,20,45,46).

Viral factors

Individuals who develop drug-resistant mutations of HIV can transmit those mutations to others in the community. This leads to pretreatment drug resistance among individuals naïve to ART. Unfortunately, those with pretreatment drug resistance are more susceptible to virological failure and further development of resistance after initiating NNRTI-based ART (17,47-49). In addition, some HIV subtypes are more likely to give rise to HIVDR than others (20).

Table 1 Strategic objectives of the WHO Global Action Plan on HIVDR 2017–2021

Objective	Description
Prevention and response	Countries are encouraged to implement high-impact interventions to prevent and respond to HIVDR, such as treat all regardless of a patient's CD4 count, implementation of PrEP, and transitioning to dolutegravir for first-line ART
Monitoring and surveillance	Policy decisions should be informed by data on HIVDR prevalence and trends. As such, the WHO recommends that countries conduct nationally representative surveys of HIVDR periodically. At the individual patient level, treatment decisions should be based on data such as routine viral load and HIVDR testing. It is therefore important to expand the coverage and quality of routine viral load and HIVDR testing to inform continuous HIVDR surveillance Programme indicators can act as early warning signs of HIVDR. Monitoring the quality of service delivery through routinely collecting indicators such as on-time pill pick up, retention on ART at 12 months, drug stock-out, viral load suppression, viral load testing, and appropriate switches to second-line ART is useful for evaluating how effective the programme is in preventing HIVDR
Research and innovation	The WHO encourages innovative research which can lead to interventions that will have the greatest public health impact on minimizing HIVDR. There is also a need for research to fill existing knowledge gaps on the risk of HIVDR for newer antiretroviral drugs and evaluate the impact of service delivery interventions to increase viral load suppression and contain HIVDR
Laboratory capacity	To expand viral load and HIVDR monitoring in LMICs, laboratory capacity and quality must be strengthened
Governance and enabling mechanisms	Governance and enabling mechanisms are essential to support actions on HIVDR. They include strong advocacy networks within the country, coordinated actions across all stakeholders involved, the Ministry of Health having ownership and oversight of the HIV programme, and sustainable funding mechanisms

HIVDR, HIV drug resistance; ART, antiretroviral therapy; HIV, human immunodeficiency virus; LMICs, low and middle-income countries.

Strategies to address HIVDR

In recognition that addressing HIVDR is an important pillar of the global HIV response, the WHO launched the Global Action Plan on HIV Drug Resistance 2017–2021 (50). The Global Action Plan has laid out WHO's guidelines on combating HIVDR across five strategic objectives (refer to *Table 1*).

Thus far, there has been a lack of research examining Southeast Asian countries' policy responses to combat HIVDR. This study therefore aims to use the WHO Global Action Plan on HIVDR 2017–2021 strategic objectives as a framework to evaluate Southeast Asia's progress in combating HIVDR.

In summary, there has thus far been a lack of research examining the prevalence, determinants and strategic management of HIVDR in Southeast Asia. This study aimed to fill this gap by first, conducting a literature review on the prevalence of HIVDR in Southeast Asia, second, understanding the key contributing factors to HIVDR in Southeast Asia, and third, evaluating Southeast Asian countries' progress in managing HIVDR. We present the following article in accordance with the Standards for Reporting Qualitative Research (SRQR) reporting checklist (available at <https://jphe.amegroups.com/article/>

[view/10.21037/jphe-22-5/rc](https://doi.org/10.21037/jphe-22-5/rc)) (51).

Methods

An interpretive descriptive approach was taken to integrate secondary data from the literature review with primary data from the key informant interviews (52,53).

Data collection comprised literature review and semi-structured interviews with stakeholders. A literature review was conducted to collect secondary data relevant to the study objectives. This included peer-reviewed journal articles and grey literature such as reports by international organisations. We systematically searched for literature related to HIV in each Southeast Asian country published between January 1, 2009, and January 8, 2022 in PubMed, and all relevant grey literature from HIV/AIDS-related international organisations.

A total of 17 interviews were conducted with stakeholders across 10 Southeast Asian countries. Interviews were conducted by the first, second and third authors. All three were public health researchers with backgrounds in psychology (HXC), public policy (SYT), and medicine (KCK).

Participants were selected through purposive sampling using a snowball recruitment strategy. We aimed for maximum variation by seeking out a variety of stakeholders

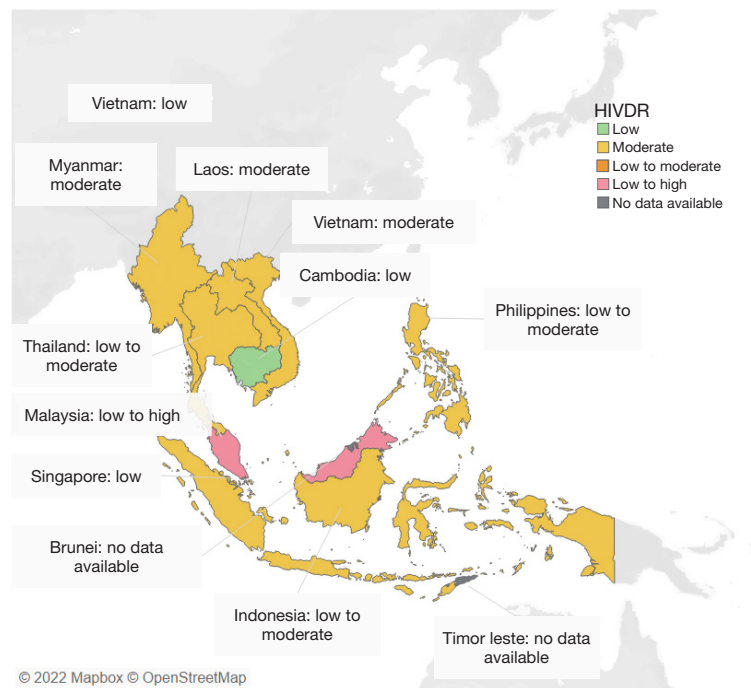


Figure 1 HIVDR prevalence in Southeast Asia. The WHO HIVDR level classification is used: low indicates <5%, moderate 5–15%, and high $\geq 15\%$ (17). HIVDR, human immunodeficiency virus drug resistance.

working in different settings related to HIV care, including government, community-based organizations, health providers, and academia. Participant characteristics are reported in the [Table S1](#). Recruitment was done over email and participants provided either written or verbal consent before the interviews. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics approval was provided by the National University of Singapore Saw Swee Hock School of Public Health Department Ethics Review Committee (No. SSHSPH-141).

The interview topic guide was designed around our study objectives and covered: trends/patterns of HIVDR, factors causing and perpetuating HIVDR, policy strategies or interventions to address HIVDR, and recommendations/suggestions. Interviews were conducted between August to October 2021 over Zoom ([Appendix 1](#)). Interviews were not audio-recorded to protect participants' privacy and expanded notes were taken. All interview data were anonymized before being stored in a secure online platform.

Data analysis was conducted using framework analysis. Interview data was sorted according to the framework (i.e., the topics listed in the interview topic guide). Next, transcripts were coded according to an initial coding frame formulated

through the literature review. This framework was revised iteratively throughout the coding process to incorporate concepts that emerged from the qualitative coding.

We present results on HIVDR prevalence in Southeast Asia largely through our literature review, supplemented by information from our interviewees. Additionally, primary data gathered from our interviews were triangulated with secondary data from our literature review to generate several overarching themes that are largely presented in the sections “Factors causing and perpetuating HIVDR in Southeast Asia” and “Management of HIVDR in Southeast Asia”.

Results

HIVDR prevalence in Southeast Asia

Overall, HIVDR prevalence was low to moderate in the region. *Figure 1* summarises the HIVDR prevalence in Southeast Asia.

Brunei

There was no published data available on HIVDR

prevalence in Brunei. Indeed, the Bruneian key informant (IDI17) noted that there is no proper surveillance system for HIVDR in Brunei as they do not have the capabilities to perform HIVDR testing within the country. Anecdotally, a rise in HIVDR has been observed, mostly cases of resistance to NNRTI (IDI17). IDI17 estimated that 2–3% of patients fail first-line ART, usually those who are ART-experienced.

Cambodia

A few studies have examined HIVDR in Cambodia. Overall, HIVDR prevalence was low among Cambodian adults. Among antiretroviral drug-naïve PLHIV in Cambodia, TDR was reported to be 1.49% in 2007 (54). Another survey in Phnom Penh conducted among PLHIV adults receiving triple combination ART reported that 2.6% were resistant to both NRTIs and NNRTIs (55). Among PLHIV attending a Phnom Penh HIV clinic between 2010 to 2012, 12.9% had virological failure, of which 86.3% of the viremic patients sequenced were found to have at least one drug-resistant mutation (DRM) (56). For antiretroviral drug-naïve PLHIV, the prevalence of DRMs was 4.9% (57). However, Cambodian children failing first-line antiretroviral therapy were found to be at extremely high risk of HIVDR. 98% were found to have HIVDR, and concerningly, the 2010 WHO pediatric monitoring guidelines failed to detect viral failure in this group (58,59).

Indonesia

In 2021, the WHO reported that Indonesia's national prevalence is low to moderate (PDR any NRTI 4.0%, NNRTI efavirenz/nevirapine 6.5%, doravirine 5.2%, etravirine 3.2%, rilpivirine 6.4%) (14).

In recent years, many studies have been conducted on HIVDR in Indonesia. Most individual studies have been conducted with small sample sizes of 30–40 PLHIV, so caution should be taken in interpreting the prevalence rates reported.

Low HIVDR prevalence has been reported in Jakarta (TDR 4.65%) (60) and Surabaya (TDR for reverse transcriptase inhibitors 4.3%) (61). Similarly, in Kepulauan Riau, the prevalence of major DRMs against NRTIs or NNRTIs was 2.2% (62). Results are mixed in Bali. In Buleleng, Bali, TDR for reverse transcriptase inhibitors was reported to be 16.7% (63), while a separate study detected 10% prevalence of major DRMs against NRTI or NNRTI

in their sample (64). However, a study in Denpasar, Bali did not detect any TDR (65). Other locations have reported high HIVDR rates. In a study of 105 PLHIV across various Indonesian cities, 20% were found to have major DRMs against NRTIs or NNRTIs (66). In North Sulawesi, 23.7% were found to have major DRMs against NRTIs or NNRTIs (67). In Pontianak, ADR was 28.5% but TDR was 0% (68). In Maumere, 13% of the PLHIV sampled had major DRMs against NRTIs or NNRTIs (69). West Papua reported 12.9% prevalence of major DRMs against NRTIs or NNRTIs (70).

HIVDR seemed to be more prevalent in key populations. The prevalence of HIVDR for PLHIV who inject drugs in Jakarta was reported to be 24.1% (71).

Lao PDR

Not much data was available on HIVDR in Lao PDR. One study which sampled PLHIV visiting a hospital in Vientiane, the capital of Lao PDR, in 2012 found a moderate HIVDR prevalence of 11.5% (72).

Malaysia

While no national prevalence data was available for Malaysia, several studies have been conducted, largely in Kuala Lumpur. All studies in Kuala Lumpur have reported low HIVDR prevalence. Two studies in Kuala Lumpur did not detect any TDR, one with a sample of HIV-positive blood donors (73), the other with a group of treatment-naïve PLHIV presenting at an infectious diseases clinic (74). Similarly, Tee *et al.* reported that only 1% of antiretroviral drug-naïve PLHIV they tested in Kuala Lumpur had any major mutations conferring drug resistance (75). Among key populations, TDR was not detected in a study of 87 MSM in Kuala Lumpur (76). As for other parts of Malaysia, a study testing ART-naïve HIV patients across Peninsular Malaysia found moderate to high prevalence of TDR (NRTI 7.5%, NNRTI 17.5%, protease inhibitors 17.5%) (77). Similarly, moderate TDR (14.3%) was detected among prisoners in Kelantan (78). Taken together, the studies suggest that HIVDR may be low in Kuala Lumpur but higher in other parts of Malaysia.

Myanmar

According to national prevalence rates provided by WHO, PDR is moderate. National prevalence for PDR was 5.4%

in 2017 and 2019 (4,79). In 2021, national prevalence for PDR was 1.4% for NRTIs. For NNRTIs, national PDR prevalence was 3.9% efavirenz/nevirapine, 1.6% doravirine, 1.8% etravirine, and 5.4% rilpivirine respectively (14). For those with prior antiretroviral drug exposure, PDR prevalence was high (15.7%, 2019) but TDR among those who were treatment-naïve was low (4.3%, 2019) (4). HIVDR seems to be moderate to high among those living near the China-Myanmar border and among IDU. Ye *et al.* detected 20.1% TDR across Burmese IDU and Burmese long-distance truck drivers crossing the China-Myanmar border (80). Similarly, TDR was found to have increased significantly among Burmese youth along the China-Myanmar border from 2009 to 2017 (4.00% to 13.16%) (81). Finally, 12.80% TDR was reported in Burmese travellers crossing the China-Myanmar border at the Dehong ports (82).

Philippines

Drug-resistance surveillance conducted by the Philippines Department of Health reported a low TDR of 2.7% for drug-naïve PLHIV and moderate ADR of 9.2% for PLHIV at one year of treatment (83). Other studies have reported moderate rates of HIVDR prevalence. A study of PLHIV in Manila and Cebu who had received one year of ART noted moderate ADR (8.6% for NRTIs, 9.2% for NNRTIs) (84). Similarly, major DRMs were detected in 8.2% of treatment-naïve and experienced Filipino PLHIV seeking treatment at a hospital in Metro Manila (85). However, drug-resistant strains may be circulating among key populations. In a group of largely treatment-naïve IDU and MSM with HIV, 80.9% of them were highly resistant to NNRTI nevirapine (86).

Singapore

The Singapore Ministry of Health has been conducting HIV molecular surveillance. Except a spike in 2015, prevalence rates have remained low (TDR 2014: 3.4%, 2015: 7.0%, 2016: 3.7%, 2017: 3.1%, 2018: 3.8%) (87).

Timor Leste

No published data was available on HIVDR prevalence in Timor Leste. The Timor Leste key informant (IDI03) interviewed noted that there has not been any HIVDR or serology survey done in Timor Leste so far as there was no capability for HIVDR testing within the country.

Thailand

Many studies of HIVDR have been conducted in Thailand, and overall show low HIVDR prevalence. The national PDR prevalence rate reported by WHO in 2021 was low to moderate at NRTI 1.7%, NNRTI efavirenz/nevirapine 3.6%, doravirine 1.2%, etravirine 1.9%, rilpivirine 5.5% (14), and this low to moderate prevalence seems to have been maintained throughout the years (1.9–5.6% from 2006–2013) (88).

TDR prevalence appeared to be on the rise in the 2000s (2.0% in 2006 to 4.8% in 2013) (88). This is in line with Iemwimangsa *et al.*'s (89) observations that among PLHIV who failed treatment, rates of NRTI and NNRTI resistance increased since ART first became available in Thailand in 1999. There was then a dramatic increase in NRTI and NNRTI resistance when the Thai Universal Coverage scheme was rolled out and provision of free ART under the National Access to Antiretroviral Program for People Living with HIV/AIDS was rapidly scaled up [2007–2010] (89,90). HIVDR prevalence then declined after the HIV National Guideline was released in 2010, suggesting that the national guidelines may have aided healthcare providers in prescribing ART regimens that are more effective and easier to adhere to, reducing the development of HIVDR (89,91). Indeed, subsequent studies support this, reporting that TDR was on the decline from moderate to low prevalence in the 2010s (12.5% in 2009–2010, 7.9% in 2011–2014, 4.8% in 2017–2018) (92–95).

Among key populations, TDR among MSM in Thailand with acute HIV infections has been a concern,(96,97) especially given the high rates of HIV prevalence among MSM there, but TDR in this population has been declining over the years (12.5% in 2009–2010, 9.6% in 2011–2012, 4.8% in 2013–2014) (91).

Viet Nam

According to recent national prevalence rates provided by WHO, PDR is moderate: NRTI 3.5%, NNRTI efavirenz/nevirapine 3.4%, doravirine 10.5%, etravirine 1.8%, rilpivirine 2.4% [2021], overall PDR 5.8% [2019] (4,14). PDR prevalence was moderate (11.1%) for those with prior antiretroviral drug exposure while TDR among the treatment-naïve was low (4.6%) (4). HIVDR prevalence rates reported in 2015–2016 were higher (PDR 14.7%), but this may have been due to a smaller and not nationally representative sample (15).

ADR prevalence has been low. The WHO reported in 2019 that ADR was 3.0% for those on ART 12±3 months and 3.4% for those on ART ≥48 months (4), while in 2017, ADR was 4.6% for those on ART 36+ months (79,98). In an earlier study conducted in 2013–2014, Nguyen *et al.* reported 5.5% HIVDR in Hanoi patients on ART for at least 36 months (99).

For children, 5.15% prevalence of DRMs was detected among children beginning treatment in Ho Chi Minh (100). After 12 months of treatment, 7% had acquired DRMs (100). In contrast, 17.4% of children in Hanoi who completed 2 years of ART had acquired DRMs (101). As for key populations, an alarmingly large proportion of PLHIV in key populations living in central Viet Nam had DRMs (32.5% overall, 47.4% for IDU, 33.3% for MSM, 8.3% for female sex workers) (102). In northeast Viet Nam, HIVDR prevalence was moderate among IDU (HIVDR 13.4%) (71). Meanwhile, in north Viet Nam, TDR levels reduced from high to moderate from 2007 to 2012 (IDU: 35.9% to 18.6%, FSW: 23.1% to 9.8%) (103).

Factors causing and perpetuating HIVDR in Southeast Asia

Factors contributing to HIVDR in Southeast Asia have been categorised into programmatic, patient-related, and regimen- and drug-related factors. Viral factors are not included as no viral factors were mentioned as determinants of HIVDR in Southeast Asia in any of the key informant interviews.

Programmatic factors

In terms of financing, HIV testing and ART were free or heavily subsidized for citizens in all Southeast Asian countries by the government or external donors. Brunei, Cambodia, Indonesia, Myanmar, Philippines, Timor Leste, and Thailand offered free HIV testing and services. In Malaysia, ART was free but only some providers offered free testing and monitoring, so patients may have been more hesitant to attend their clinical appointments (IDI01). In Singapore, Viet Nam and Lao PDR, the cost of HIV testing and treatment was heavily subsidized and patients paid a small co-payment (104). HIV services were free for the poor. Nonetheless, patients in Singapore, Indonesia and Viet Nam noted that the cost of HIV treatment still imposed a financial burden (104–107) because finding and sustaining employment has been challenging for PLHIV

(106,108). Finding a job that allows regular absences from work and finding ways to explain these absences are difficulties that PLHIV have faced. For those working in the informal sector, missing work may mean losing their jobs or losing out on much needed income. Despite Viet Nam's transition from fully-funded ART to a co-payment model, Vu *et al.* (104) observed that HIV care remained affordable for the vast majority of Vietnamese PLHIV, and only 0.1% of PLHIV had catastrophic expenditure on HIV services.

Even in countries where ART was free, financial barriers still deterred PLHIV from accessing treatment. Key informants and secondary data in Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Timor Leste and Viet Nam highlighted that a major barrier to seeking care is geographical access and the time and cost needed to travel to the hospital or clinic (107,109–111). For example, the archipelagic and vast geography in Indonesia poses both logistic and financial barriers for some rural populations to accessing healthcare in the local community health centres. Community-based organisations (CBOs) in Cambodia have recognized this issue and provided financial and logistical support to PLHIV. Many PLHIV received travel assistance and/or lodging compensation to attend their clinical appointments (112). If they are hospitalised, daily allowances may be given. CBOs also strengthened PLHIV's financial situation by providing small amounts of money and assisting PLHIV to develop income-generating activities such as producing handicraft and raising livestock (112). Other initiatives that Cambodian CBOs have worked on include bringing ART to the community. A community representative could visit the ART clinic every two months and bring back medicine on behalf of their peers, reducing time and travel costs.

The time and money needed to travel to the clinic was a heavy burden for PLHIV who are impoverished and living in rural areas, particularly in countries which had drug stock-outs and/or did not practice multi-month drug dosing (113). Drug stock-outs were raised as an issue in Indonesia, Lao PDR, Myanmar and Timor Leste (114). A lack of multi-month drug dosing was highlighted for Cambodia and Timor Leste. IDI03 shared that Timor Leste faces significant problems with ART availability due to supply chain issues. The forecasting of demand for ART drugs has not been accurate, leading to drug stock outs. Even after the ART drugs arrived at the central warehouse, bureaucratic processes prevented healthcare providers from getting approval to collect the ART drugs. Due to the shortage of drugs, almost all clinics dispensed ART month-by-month.

The lack of patient confidentiality was another barrier that deterred PLHIV from seeking and continuing treatment. In Indonesia, a major deterrent for PLHIV to receive free HIV services was the approval required from the neighbourhood head, which necessitated that the patients disclose their HIV statuses to their neighbourhood head. In Brunei, anonymous HIV testing was not available, discouraging people from coming forward to get tested. In Philippines and Timor Leste, key informants observed that some patients were discouraged from attending clinics due to the lack of private spaces in clinics and some healthcare providers had failed to maintain patient confidentiality. As such, it was easy for news about who had visited the HIV clinic to spread in the community. To get around this, IDI03 shared that the patients might cut ART medications into half to share with their family so that their family member did not have to see a doctor and disclose their HIV status. This led to sub-optimal drug regimens and fostered HIVDR.

Patient confidentiality was also an emerging problem in Viet Nam as it moved towards decentralising HIV services from central urban hospitals to local clinics/hospitals. The biggest concern raised by Vietnamese PLHIV about HIV service decentralization has been about keeping their HIV statuses confidential if they were seen regularly visiting the local HIV clinic (105). The other issue with decentralizing HIV services in Viet Nam has been that many local clinics/hospitals did not have sufficient capacity or experience in delivering HIV services, including a lack of viral load monitoring capacity. Patients used to receiving ART at urban hospitals expressed concerns about the low quality of HIV care at local health facilities (105).

Health system processes which were not patient-friendly hindered treatment access and adherence. In Lao PDR, HIV services were not well-integrated, resulting in patients dropping out of treatment (115). PLHIV in Viet Nam were frustrated with the lack of clarity and consistency on how to access ART, with some were required to attend many clinics or pay to get re-tested before they were able to access ART (116). Vietnamese caregivers of children with HIV reported that clinic appointments were fixed on school days so children could not come to clinic, but caregivers were not allowed to collect ART drugs on the child's behalf (110). In Malaysia, IDI01 shared that the patients cannot receive medication unless they have a fixed address, meaning that homeless PLHIV were not able to collect ART medication. While previously ART medication used to be collected by an outreach worker and given to homeless patients when they visited the drop-in centres, this was no longer possible

after drop-in centres closed due to budget constraints.

Myanmar has been in a unique situation because the military coup resulted in much upheaval and uncertainty in their healthcare landscape. IDI14 shared that one of their biggest challenges is the shortage of healthcare workers, especially doctors and nurses, as many healthcare workers joined the Civil Disobedience Movement and some were arrested and died. Access to testing and treatment were heavily impacted due to the closure of some government hospitals and clinics. Many PLHIV did not know where they could go for testing and treatment, and some even had to travel to other towns or states to reach the nearest ART provider. As key populations participated in the political movement and were prone to harassment by security forces, many were not able to travel to access HIV services due to security concerns. IDI14 noted that viral load monitoring coverage was good (>70%) prior to the military coup, but after the coup only targeted viral load testing was available. The supply of ART drugs also became limited to the government-run National AIDS Programme. IDI12 noted that there was no proper HIV service provision in the Ethnic Armed Controlled areas, particularly along the southeast border. While the Myanmar government has been funding ART, there has been much uncertainty after the military coup and key informants were unsure if ART would continue to be funded. Amidst the political upheaval, non-governmental and community-based organisations involved in the HIV care cascade have been vital in bridging the gap to provide more testing and treatment. IDI14 noted that there were many limitations arising from the political situation, such as politically driven refusal to communicate between stakeholders. As such, NGOs faced challenges in obtaining approval to provide field services and accessing commodities required for HIV services. Overcoming political differences and partnering between the public and private sectors are thus essential to ensure continuity of HIV services in Myanmar.

The important role of CBOs in supporting PLHIV was emphasized not just in Myanmar but also in other countries. In Indonesia, CBOs were vital in reaching hidden key populations. In Lao PDR, support groups run by CBOs such as the Lao PDR Youth Association of PLHIV and the Red Cross were a resource for PLHIV to overcome adherence and other HIV-related issues (109). Cambodia's strong support for PLHIV included community- and hospital-based support groups, home visits and adherence counselling to engage and educate PLHIV at each touchpoint (112).

Patient-related factors

For patient-related factors, key informants noted that non-adherence and lost to follow up were the main contributing factors to HIVDR (20,117-120). Among MSM in Philippines, 12.4% to 21% were non-adherent (121,122). In Thailand, adherence among PLHIV seemed to be poor across studies examining PLHIV in general, adolescents and key populations (e.g., MSM, transgender women), reporting 37.4% to 48.4% poor adherence (123-125). In Viet Nam, suboptimal adherence rates ranged from 8% among PLHIV with a history of drug use to 54.5% in the general PLHIV population (126,127).

Treatment drop-out was also significant in Indonesia and Timor Leste. In Indonesia, about one quarter were lost to follow up, and resulted in subsequent virological failure and needing to go to second or third-line ART (128,129). In Timor Leste, motivation to adhere to treatment was low and dropout was very high, with historical drop out rates of up to 80% (IDI03). IDI03 observed a strong belief in the community that HIV was fatal because historically, HIV mortality was high when ART was not consistently available. However, this has been improving with education and counselling to reduce stigma and discrimination by the community and healthcare workers. Lost to follow up was also high among youth, ranging from 11% to 28% among children and teenagers in Thailand (130-132) and 13% to 25% in Myanmar (120). IDI08 observed that the transition from childhood to adolescence was challenging for PLHIV. Children may stop being adherent when they reached adolescence for various reasons, from wanting to hide their HIV status from their partners to running away from home. In contrast, drop out rates were lower among adults in Viet Nam, Thailand and Myanmar. In Thailand, loss to follow up was about 10.2% to 12.8% across patients enrolled in the National AIDS Program (133) and 9.6% for MSM (134). In Myanmar, prior to the military coup, lost to follow up ranged from 7% to 12% for adults (118,119,135). In Viet Nam, the drop out rate was 14% after two years of ART (113).

Non-adherence stems from several factors. First and foremost, stigma is prevalent and one of the main barriers preventing PLHIV from seeking and adhering to treatment across all countries in the region (109,115,136-150). The stigma PLHIV encountered made them feel depressed, isolated and unmotivated to adhere to ART (109). Several Southeast Asian countries criminalised key populations, including Brunei, Indonesia, Malaysia and Singapore. These laws acted to keep key populations hidden and further entrenched stigma against key populations (151).

In Malaysia, while laws against MSM were not enforced, IDI13 observed that stigma against MSM, transgender and sex workers has worsened in the last decade, with transgenders and sex workers fearing threats of violence. Concerningly, Indonesia has taken a hardline stance against key populations. The closing of designated sex work areas resulted in sex workers shifting to operate covertly online, making it harder for them to access HIV prevention and care (151). Similarly, the police have been applying anti-pornography laws, public order laws and the Sharia criminal code to crackdown on the LGBT population in Indonesia (151,152). Likewise, crackdowns on drug use in Cambodia and Philippines resulted in mass arrests and human rights violations, pushing drug users into hiding (151). In Malaysia, IDI13 noted that stigma against drug users has lessened after the government shifted its approach from a criminal justice stance to a public health paradigm, but drug users remain fearful that coming forward for HIV testing and treatment might expose them, causing them to be arrested.

Besides legal enforcement, stigma from the community actively hindered PLHIV from adhering to treatment, fearing that their HIV status might be discovered if they were seen at the HIV clinic or seen taking medication (109,140,148,153). In Indonesia, some patients provided fake addresses to the healthcare providers as they did not want their neighbours to know that they were being monitored by the hospital, making it difficult for healthcare workers to follow up with them (IDI04). Finally, stigma from healthcare workers was a major deterrent to PLHIV seeking care and has been noted in Lao PDR, Philippines, Timor Leste and Viet Nam (114,145,152-154) (IDI03, IDI11). In Timor Leste, IDI03 observed instances where persons asking for a HIV test or condoms were turned away by the midwife at the clinic because they were not married. In the Philippines, the naming of HIV clinics as “social hygiene clinics” was noted to be stigmatising and poor bedside manner from healthcare providers also led PLHIV to drop out from treatment (IDI11). At the same time, Filipino HIV care providers expressed uncertainty on how to be sensitive to patient gender and sexuality (155), and Vietnamese HIV care providers were reticent to discuss sexual identity and same-sex relationships, resulting in their failure to explore risk factors for HIV and inadequate client-centred counselling (116). This underscores the need to train healthcare providers to engage key populations and deliver services sensitively.

Besides stigma and discrimination, PLHIV's occupation emerged as a contextual factor influencing treatment

adherence. Migrant workers, those who travel for work, and informal economy workers were more likely to be non-adherent. Many Cambodian and Laotian migrant workers moved to Thailand for work and faced a shortage of medicine but were not able to return regularly to their home countries to refill their ART prescriptions (109). This was exacerbated by the fact that Cambodia does not practice multi-month dispensing of ART drugs. Although Thailand offered migrant health insurance providing free ART and HIV care, implementation was challenging. Only certain hospitals agreed to provide services to migrant workers, and the insurance was only available to those who legally reside in Thailand. However, many Cambodian and Laotian migrant workers working in the informal sector did not register their migrant status and were therefore ineligible for free HIV treatment. Communication about the migrant health insurance scheme was very confusing, resulting in a lack of trust and understanding in this system (IDI10). There is a need for CBOs to support migrant workers in registering their migrant status and obtaining health insurance.

Internal migrant workers in Indonesia faced similar difficulties accessing ART. As funding for the Community Health Centres came from the provincial government, some provinces were strict that only those who were domiciled in this area could access the Community Health Centres there. However, in Jakarta, residents could access Community Health Centres and hospital services as long as they could prove that they live in Jakarta.

Besides migrants, those working in the informal economy were not entitled to sick leave and could lose their job if they missed work, leading to non-adherence (IDI02). Similarly, fishermen were also more likely to miss appointments, have poor medication compliance and be lost to follow up because they were at sea (113).

Mental illness and substance dependence among PLHIV also undermined patients' ability to adhere to treatment, contributing to drug resistance (156-159). This is a concern in Viet Nam (158,160), where PLHIV have high prevalence of depressive symptoms (ranging from 20% to 40%) and HIV-associated dementia (ranging from 11% to 39.8%) (160-163). Among IDU with HIV, the prevalence of depression was even higher at 69% (164). This is in line with studies of PLHIV globally which reported mental health symptoms in 28% to 62% of PLHIV (165). It is vital to treat mental health, neurocognitive and substance use issues to improve treatment adherence and PLHIV's quality of life.

Lastly, a lack of knowledge about HIV was observed to undermine treatment initiation and adherence in Brunei,

Lao PDR, Malaysia, Philippines, Timor Leste and Viet Nam (107,166). For example, in Viet Nam, many children with HIV were cared for by their grandparents or relatives because their parents had passed away. These caregivers shared that they did not have knowledge about HIV or its treatment, and might not know the importance of taking accurate doses of ART on time (110). In Timor Leste, IDI03 noted that there is very little knowledge of HIV among the general population, and NGO efforts to educate the public were challenged by religious norms. Bruneian key informants shared that while the MSM population were much more aware about HIV, non-MSM and older people tended to lack knowledge of HIV. In Lao PDR, reluctance to get tested and seek HIV treatment was also highlighted among the general population, MSM and female sex workers due to a lack of knowledge about sexual health and healthcare services available and low risk perception despite engaging in high-risk sexual behaviours (115,141,142). Misinformation about HIV was also noted as a barrier. IDI11 shared that in isolated areas in the Philippines without TV or internet, beliefs that HIV can be transmitted through mosquito bites were still present. In Malaysia, some PLHIV were not keen on taking ART as they believed in using traditional or alternative medicine to treat HIV.

Regimen- and drug-related factors

One factor highlighted by key informants was limited ART options. In Lao PDR, only first- and second-line ART were available. Bruneian key informants shared that despite extensive treatment counselling, some patients were not adherent to treatment due to intolerance to the ART drugs given. However, as Brunei has limited ART options available, the ability of clinicians to switch ART regimens for such patients was constrained. Some healthcare providers in Philippines switched patients who were intolerant to first-line regimens to dolutegravir (IDI16). IDI17 noted that the Bruneian government may consider bringing in dolutegravir for this reason.

For children, ART options were even more limited, and if powder or suspension drugs were not available, their medication had to be cut from adult tablets. This made it challenging to ensure that the dose was right, particularly as their caregivers may be grandparents who were not well-educated and did not understand the correct doses to give (IDI08).

Historically, NNRTI-based first-line regimens have been mostly used in Southeast Asia as they were considered the gold standard and were inexpensive. These antiretroviral

drugs have a very low genetic barrier to resistance. As such, there is a very thin cushion between missing medication doses and treatment failure, and then drug resistance (IDI02). Patients who miss their medications were at risk of developing HIVDR to NNRTIs efavirenz and nevirapine. Efavirenz has a very low genetic barrier to resistance and a very long half life, resulting in subtherapeutic levels of efavirenz lingering in patients' systems, further exerting selection pressure on the virus. These factors have resulted in efavirenz resistance lingering on in the population. For countries such as Thailand and Timor Leste which are moving towards first-line integrase-based regimens (i.e., dolutegravir), NNRTI resistance would be less of a concern.

Management of HIVDR in Southeast Asia

Prevention and response

With the exception of Brunei and Indonesia, all Southeast Asian countries have adapted the 2018 or 2021 WHO consolidated guidelines on antiretroviral drug use for treating and preventing HIV infection and introduced dolutegravir into their national guidelines (167). While dolutegravir was already available in Cambodia, Philippines, Singapore and Timor Leste, other countries were either in the process of procuring dolutegravir or have delayed its procurement. Several key informants noted that governments were busy focusing on managing COVID-19 so HIV and other public health issues were put on the back burner, including the procurement of dolutegravir.

Barriers to incorporating dolutegravir into first-line regimens included higher cost. IDI13 reported that Malaysia was still using NNRTI-based ART regimens which do not have a good genetic barrier to resistance because the upper-middle income country was not eligible to receive generic or special-priced dolutegravir. As there was a significant cost increase of US\$50–70 a month to switch to dolutegravir, Malaysia chose to continue using inexpensive generic NNRTI options and would only consider dolutegravir if generic dolutegravir became available. Because ART regimens in Malaysia have been limited to a few NNRTIs such as efavirenz and nevirapine, there were still other ART options Malaysia could turn to if the patient has HIVDR. Similarly in Singapore, the cost of abacavir/dolutegravir/lamivudine (recommended by national and international guidelines as first-line regimen) was US\$285 per month before government subsidy. This was much more expensive than other ART options such as abacavir/lamivudine in combination with efavirenz (US\$81.40) (IDI15).

Monitoring and surveillance

Singapore and Thailand made excellent progress in monitoring and surveilling HIVDR, having conducted nationally representative HIVDR surveys, offered HIVDR testing to those who need it, achieved $\geq 70\%$ viral load coverage, and routinely monitored program quality indicators (167).

Most countries in the region had conducted nationally representative HIVDR surveys even if they did not have local capacity to conduct HIVDR testing, as technical assistance was given by the WHO (167). Insufficient or absent HIVDR testing capacity within the country was a major bottleneck preventing Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar and Timor Leste from offering HIVDR testing to patients who needed it. Although Brunei offered HIVDR testing to patients who have virological failure or are non-adherent, it lacked the capability to do HIVDR testing locally and had to send samples overseas, which resulted in delays to receiving test results.

While viral load testing coverage was good in Brunei, Cambodia, Singapore, and Thailand ($\geq 70\%$), viral load testing coverage needs to be scaled up in the other countries, particularly in Indonesia which only had 17% viral load testing coverage (167).

Only five out of the eleven Southeast Asian countries routinely monitored program quality indicators (Indonesia, Myanmar, Singapore, Thailand and Viet Nam) (167). Countries' performances on early warning indicators associated with the emergence of HIV drug resistance have been regularly reported by the WHO (14). Results indicated that for viral load testing coverage and viral load suppression, Cambodia, Myanmar and Thailand have been doing well, achieving $\geq 70\%$ viral load testing coverage and $\geq 90\%$ viral load suppression. In contrast, Indonesia, Malaysia, Philippines, and Viet Nam have not managed to achieve 70% viral load testing coverage. Retention on ART at 12 months was high for Viet Nam and Myanmar (pre-military coup) at $>85\%$, but less than ideal in Cambodia and Philippines (75–85%). The drop out rate in Malaysia was concerning, with at least 25% of PLHIV on ART dropping out within the first 12 months. For drug stock-outs, Philippines reported experiencing at least one drug stock-out in 2020, while drug supplies were reported to be adequate in Cambodia, Indonesia, Malaysia, Myanmar and Viet Nam over 2017–2020. Finally, Cambodia, Malaysia and Thailand were able to offer at least 5% of PLHIV second-line ART, whereas ART options were limited in Indonesia, Myanmar and Philippines with less than 5% of PLHIV

receiving second-line ART.

Research and innovation on HIVDR

Most countries have conducted some research on HIVDR, be it HIV genotyping or surveys of HIVDR prevalence. Thailand in particular has built robust research experience over the past two decades. There was a notable lack of research in Brunei, Timor Leste and Lao PDR on HIVDR. For Timor Leste, IDI03 explained that there was a general preference for the Timorese to build their own research capabilities instead of engaging foreign experts to conduct medical research.

Laboratory capacity for HIVDR testing

Most countries in Southeast Asia had at least one laboratory that can conduct HIVDR testing, with the exceptions of Brunei, Myanmar and Timor Leste (168). Notably, the region had five WHO-designated HIV drug resistance laboratories—two each in Viet Nam and Thailand, and one in Indonesia (169). Nonetheless, genotypic resistance testing capacity remains a key bottleneck in the region. Limited laboratory capacity, expertise and high capital and test costs for resistance testing has meant that most countries could not offer this test routinely to patients with virological failure or non-adherence (170,171).

Governance and enabling mechanisms

Almost all countries in the region had national strategies for HIV and HIV monitoring and evaluation (167). The exception is Brunei which was in the midst of drafting its first National Strategic HIV/AIDS and STI Plan (IDI17). While Timor Leste had a national HIV strategy, IDI03 observed that it was not implemented on the ground.

Table 2 summarises the progress of each Southeast Asian country on the WHO Global Action Plan on HIV Drug Resistance 2017–2021, while *Table 3* summarises the findings for each Southeast Asian country on HIVDR prevalence, key factors causing HIVDR, and management of HIVDR.

Discussion

Overall, HIVDR prevalence was low to moderate in Southeast Asia. HIVDR was more prevalent among key populations such as IDU, MSM, prisoners, female sex

workers, as well as children and those living along country borders. This may be because factors contributing to HIVDR prevalence exerted a stronger effect on these groups. For example, key populations experienced “double stigma” with their HIV statuses and their identities, which undermined their willingness to disclose their statuses to access care and adhere to treatment. Children also faced additional barriers in adhering to care because of their caregivers’ lack of HIV knowledge and the tumultuous experiences of discovering and coming to terms with their HIV statuses while transitioning to adolescence. Those living in border regions were at higher risk of HIVDR likely due to the high volume of cross-border movements facilitating the transmission of HIV strains with drug-resistant mutations (173).

For factors contributing to HIVDR, geographical inaccessibility which includes the high cost and time taken to travel for treatment emerged as a major barrier in seven out of the eleven Southeast Asian countries covered. Financial barriers continued to be an issue even though HIV care was either free or heavily subsidised across Southeast Asia. PLHIV tended to be one of the most impoverished and marginalised groups, with many unable to afford even the cost of transport to attend clinic appointments or pick up their medications. This burden on PLHIV was exacerbated in Cambodia and Timor Leste where clinics did not offer multi-month drug dosing. The second major barrier highlighted across all countries was stigma. This drove non-adherence and drop outs from HIV treatment due to the fear of exposure of their HIV status, particularly as measures to protect patient confidentiality appeared to be lacking in many Southeast Asian countries. The third key finding was that labour movement within a country or across countries impeded access to HIV care as international migrant workers were mostly not eligible for or did not know how to obtain free or subsidised HIV services in other countries.

In general, governments’ commitment to addressing HIVDR have been strong, with almost all countries having set out their national strategies, monitored their HIV indices, conducted nationally representative HIVDR surveys, and aligned their national ART guidelines with the WHO guidelines. However, implementation of these plans and guidelines remains a challenge. Most of the countries in the region were still struggling to reach 70% viral load testing coverage and did not have the laboratory capacity nor financial means to offer HIVDR testing to those who need it. Furthermore, only four out of the eleven countries

Table 2 Progress on the WHO Global Action Plan on HIV Drug Resistance 2017–2021

Prevention and response	Monitoring and surveillance				Research and innovation on HIVDR				Governance and enabling mechanisms		
	Adapted 2018 or 2021 WHO consolidated guidelines on antiretroviral use for treating and preventing HIV infection	Dolutegravir introduced into national guidelines	Dolutegravir available as treatment option	Nationally representative HIVDR surveys	HIVDR testing	Viral load testing coverage	Routine monitoring of program quality indicators	Research and innovation on HIVDR	Laboratory capacity for HIVDR testing	Has national strategy for HIV monitoring and evaluation	Has national strategy for HIV monitoring and evaluation
Brunei	x	x	x	x	√	√	x	x	x	+ (draft of first National Strategic HIV/AIDS and STI Plan in progress)	x
Cambodia	√	√	√	x	x	√ (≥70%)	x	√	√	√	√
Indonesia	x	x	x	√	x	+ (17%)	√	√	√	√	√
Lao PDR	√	√	+ (procurement initiated)	x	x	+ (only for selected populations and situations)	x	+ (only 1 study conducted)	√	√	√
Malaysia	√	√	+ (procurement initiated)	√	x	+ (<70%)	No data available	√	√	√	No data available
Myanmar	√	√	+ (procurement delayed)	√	x	+ (>70% in 2020 but since military coup only targeted testing available)	√	√	x	√	√
Philippines	√	√	√	√	√	+ (<70%)	x (not since 2017)	√	√	√	√
Singapore	√	√	√	√	√	√ (100%)	√	√	√	√	√
Thailand	√	√	+ (procurement delayed)	√	√	√ (≥70%)	√	√	√	√	√
Timor Leste	√	√	√	x	x	+ (50%)	No data available	x	x	+ (yes but not implemented)	√
Viet Nam	√	√	+ (procurement initiated)	√	No data available	+ (<70%)	√	√	√	√	√

Sources: (14,56,89,167,168,172). Adapted 2018 or 2021 WHO consolidated guidelines on antiretroviral use for treating and preventing HIV infection: √, yes; x, no. Dolutegravir introduced into national guidelines: √, yes; x, no. Dolutegravir available as treatment option: √, yes; +, no, but there are plans to procure; x, no. Nationally representative HIVDR surveys: √, has conducted at least one nationally-representative HIVDR survey; x, no nationally-representative HIVDR surveys have been conducted yet. HIVDR testing: √, HIVDR testing is available to PLHIV who have treatment failure; x, HIVDR testing is not available. Viral load testing coverage: √, meets UNAIDS target of at least 70% of eligible PLHIV receiving at least one annual viral load test; +, less than 70% of eligible PLHIV receive at least one annual viral load test. Routine monitoring of programme quality indicators: √, yes; x, no. Research and innovation on HIVDR: √, studies on HIVDR have been conducted in the country; +, one study on HIVDR has been conducted in the country; x, no research on HIVDR has been conducted in the country. Laboratory capacity for HIVDR testing: √, at least one laboratory in the country has capacity to do HIVDR testing; x, no laboratory in the country can perform HIVDR testing. Has national strategy for HIV: √, yes; +, draft in progress; x, no. Has national strategy for HIV monitoring and evaluation: √, yes; x, no. HIVDR, HIV drug resistance.

Table 3 Country summary for HIVDR prevalence, key factors causing HIVDR, and management of HIVDR

Country	HIVDR prevalence	Key factors causing HIVDR			Management of HIVDR
		Programmatic factors	Patient-related factors	Regimen- and drug-related factors	
Brunei	Unclear due to lack of surveillance system	Anonymous HIV testing not available	Stigma; criminalisation of key populations; non-MSM and older people tend to lack knowledge about HIV	Limited ART options; the use of NNRTI-based regimens which have a low genetic barrier to resistance	Lags behind in most management aspects, except for good viral load and HIVDR testing coverage
Cambodia	Low among adults but very high among children failing first-line ART	Geographical access, travel time and cost are major barriers; lack of multi-month drug dosing	Stigma; crackdowns on drug users	The use of NNRTI-based regimens which have a low genetic barrier to resistance	Good management in the aspects of prevention and response, research and laboratory capacity, and governance. While viral load testing coverage is good, other key aspects of monitoring and surveillance need further strengthening (HIVDR surveillance and testing and routine monitoring of program quality indicators)
Indonesia	National prevalence is low to moderate, but high prevalence noted in certain cities and in key populations	Geographical access, travel time and cost are major barriers; drug stock-outs; lack of patient confidentiality	Stigma; significant rates of non-adherence and lost to follow up; criminalisation of key populations; internal migrants have difficulty accessing treatment	The use of NNRTI-based regimens which have a low genetic barrier to resistance	Performance is mixed. Nationally representative HIVDR surveys and routine monitoring of program quality indicators are conducted, and there is good management of research, laboratory capacity and governance. However, viral load and HIVDR testing coverage is poor, and prevention and response measures need to be strengthened
Lao PDR	Lack of data. Moderate prevalence reported by one study	Geographical access, travel time and cost are major barriers; drug stock-outs; HIV services not well-integrated	Stigma, including from healthcare workers; general population, MSM and female sex workers lack knowledge about sexual health and healthcare services available and have low risk perception despite engaging in high-risk sexual behaviours	Limited ART options; the use of NNRTI-based regimens which have a low genetic barrier to resistance	While there is good management in most areas, Lao PDR is significantly lacking in monitoring and surveillance (viral load and HIVDR testing coverage, HIVDR surveillance, and routine program quality indicators)
Malaysia	Low in the capital Kuala Lumpur, but some studies in other parts of Malaysia have reported moderate to high prevalence	ART is free but only some healthcare providers offer free testing and monitoring; geographical access, travel time and cost are major barriers; medication collection requires a fixed address, meaning homeless PLHIV are unable to collect ART	Stigma; criminalisation of key populations; some believe in using alternative or traditional medicine to treat HIV rather than ART	The use of NNRTI-based regimens which have a low genetic barrier to resistance	Good management in most areas, but viral load and HIVDR testing coverage are suboptimal
Myanmar	National prevalence is moderate but moderate to high among those living near the China-Myanmar border and among IDU	Geographical access, travel time and cost are major barriers; drug stock-outs; health system breakdown due to the military coup	Stigma; significant rates of non-adherence and lost to follow up	The use of NNRTI-based regimens which have a low genetic barrier to resistance	Pre-existing management of HIVDR was good, but capacity to conduct viral load testing has been significantly impacted by the health system breakdown after the military coup

Table 3 (continued)

Table 3 (continued)

Country	HIVDR prevalence	Key factors causing HIVDR			Management of HIVDR
		Programmatic factors	Patient-related factors	Regimen- and drug-related factors	
Philippines	National drug-resistance surveillance reported low TDR and moderate ADR. However, high TDR has been observed in key populations	Lack of patient confidentiality	Stigma, including from healthcare workers; significant rates of non-adherence and lost to follow up; crackdowns on drug users; those living in remote areas of the country lack knowledge on HIV as there is no internet or TV access	The use of NNRTI-based regimens which have a low genetic barrier to resistance	Good performance on all management indicators except for suboptimal viral load testing coverage and lack of routine monitoring of program quality indicators
Singapore	National HIV molecular surveillance indicates low prevalence rates	No factors were raised	Stigma; criminalisation of key populations	The use of NNRTI-based regimens which have a low genetic barrier to resistance	Good performance on all management indicators
Thailand	National prevalence is low to moderate. Prevalence among MSM has been declining and is now low	No factors were raised	Stigma; significant rates of non-adherence and lost to follow up; international migrant workers have difficulty accessing treatment in Thailand	No factors were raised	Good performance on all management indicators, except for the delay in making dolutegravir available in the country
Timor Leste	Unclear due to lack of surveillance system	Geographical access, travel time and cost are major barriers; significant supply chain issues leading to drug stock-outs; lack of multi-month drug dosing; lack of patient confidentiality	Stigma, including from healthcare workers; significant rates of non-adherence and lost to follow up; little knowledge about HIV among the general population	No factors were raised	While management of prevention and response was good, all other management aspects need to be strengthened
Viet Nam	National prevalence is moderate, but prevalence among key populations is moderate to high	Geographical access, travel time and cost are major barriers; concerns about maintaining patient confidentiality and access to HIV services as HIV services are being decentralised from urban hospitals to local clinics/hospitals; lack of clarity and consistency on how PLHIV can access ART; caregivers not allowed to collect ART on the child's behalf	Stigma, including from healthcare workers; significant rates of non-adherence and lost to follow up, in part due to mental illness and substance dependence; lack of knowledge about HIV among caregivers of orphans with HIV	The use of NNRTI-based regimens which have a low genetic barrier to resistance	Good performance on most management indicators, except for viral load testing coverage and the procurement of dolutegravir

The WHO HIVDR level classification is used: low indicates <5%, moderate 5–15%, and high ≥15% (17). HIVDR, HIV drug resistance; ART, antiretroviral therapy; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PLHIV, people living with HIV; TDR, transmitted HIVDR; ADR, acquired HIVDR.

Table 4 Recommendations to manage HIVDR in Southeast Asia

Recommendation	Details
Reduce stigma and discrimination	Reduce stigma and discrimination against PLHIV among the community and healthcare workers. This includes engagement and education, the enactment of anti-discrimination laws and repealing of laws which criminalise key populations. For countries which already have anti-discrimination laws, attention should be paid to enforcement and implementation of these laws
Improve geographical access to care	Improve geographical access to care and reduce the cost and time needed to travel to health facilities. This can be done through offering client-centred, differentiated HIV service delivery and improving the convenience of medication refills through home delivery. An example of differentiated service delivery includes providing telehealth for stable patients while those requiring close follow up continue to attend in-person clinic appointments
Improve patient confidentiality	Improve patient confidentiality at health facilities by training healthcare workers to maintain patient confidentiality and providing private spaces at clinics
Improve migrants' access to HIV testing and treatment	Address cross-border transmission of drug resistance and acquired drug resistance by ensuring HIV testing and treatment are equally accessible to migrants. For example, universal health coverage schemes could be expanded to cover migrant workers for HIV testing and treatment. In countries where universal health coverage schemes already cover migrant workers for HIV, such as Thailand, engagement and education by community-based organisations is needed to help migrant workers leverage on the scheme
Expand viral load testing coverage to $\geq 70\%$	In countries where viral load testing coverage is less than 70%, prioritise expanding access to viral load testing so that treatment failure can be detected in a timely manner. Funding from international organisations or official development assistance may be necessary to expand this dimension of HIV care
Develop HIVDR surveillance systems at country and/or area levels	In countries where systematic HIVDR surveillance is lacking, systems should be developed to monitor HIVDR prevalence at the national and/or area levels
Initiate and expedite procurement of dolutegravir	In lower-middle income countries eligible to procure generic or special priced dolutegravir but have not done so due to procurement delays, explore ways to streamline procurement processes such as expedited drug reviews. Lessons may be learnt from how COVID-19 vaccine approval and procurement have been expedited (177,178)
Develop affordable HIVDR testing	Develop affordable options for HIVDR testing which can be scaled up in resource-limited settings, such as web-based genotype-free prediction systems (170,171)

HIVDR, HIV drug resistance; PLHIV, people living with HIV.

in the region offered dolutegravir as a treatment option as of December 2021. Understandably, the COVID-19 pandemic has delayed procurement processes. As the pandemic becomes endemic, governments should revisit public health priorities that have been set aside during the pandemic, including measures to achieve the HIV treatment cascade and manage HIVDR.

Although COVID-19 has had negative impacts on PLHIV's access to care, there have been positive advances in HIV service delivery borne out of the pandemic. These include the incorporation of digital health into HIV service delivery. In Indonesia and Lao PDR, home delivery of ART was made available for stable patients (174). In Thailand, differentiated service delivery was offered. Stable patients could choose to receive telehealth follow-up with ART delivered through the mail, or fast-track ART collection at the clinic (175). ART refill durations were also extended to

reduce the frequency that patients had to come to clinic. These measures overcome many of the barriers mentioned (e.g., time and cost of travel, fear of being seen at the HIV clinic), making it easier for PLHIV to access care and adhere to treatment (175,176).

To date, Southeast Asian countries whose HIVDR situation was concerning were Lao PDR and Myanmar. There was a lack of HIVDR monitoring and surveillance in Lao PDR so overall prevalence rates were unclear. However, the sole study conducted in the capital detected a concerning 11.5% HIVDR prevalence (72). Since viral load testing coverage was also poor, PLHIV with drug resistance were not detected in a timely manner, leading to poor viral suppression and treatment outcomes. While Myanmar has made great progress in controlling the HIV epidemic and HIVDR, this has been significantly set back by the political upheaval and resultant manpower shortage in healthcare

as well as the closures of hospitals and clinics across the country.

Considering our findings, we put forth our recommendations in *Table 4*.

This study has made contributions in reviewing the prevalence of HIVDR in Southeast Asia, identifying the key factors contributing to HIVDR in the region, and evaluating countries' progresses in managing HIVDR. We were able to obtain comprehensive qualitative data by interviewing key informants from different professions and sectors related to the HIV cascade across 10 countries in Southeast Asia. Robustness of the data was strengthened by triangulating primary and secondary data. One limitation is that the perspectives of PLHIV were not actively sought in this study. Capturing the voices of PLHIV regarding HIVDR, especially on measures to incentivise treatment adherence and address stigma and discrimination to overcome barriers to accessing HIV treatment and care would be important in future research. The second limitation is that for Brunei and Timor Leste, due to a lack of published data, HIVDR prevalence reports were based on self-reported estimates from key informants. Future research could address these gaps in Brunei and Timor Leste by conducting HIVDR prevalence studies.

Conclusions

This study has demonstrated that while HIVDR prevalence was overall low in Southeast Asia, prevalence was markedly higher in populations at risk of HIV, who also faced heavier barriers to accessing and adhering to treatment. Indeed, barriers which discouraged PLHIV from seeking and adhering to care emerged as the key determinants driving HIVDR in the region. Achieving the UNAIDS global target of maximal viral load suppression in 90% of all people receiving antiretroviral therapy will require all stakeholders to address these barriers by going back to the fundamentals of building good health systems. This includes ensuring equitable access to healthcare for migrant workers, marginalised populations such as MSM and sex workers, as well as rural residents, becoming more patient-centred in how health services are delivered, improving geographical access to care and strengthening the capacity of facilities to conduct viral load and drug resistance testing.

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Appendix 1 Interview guide

A. HIV drug resistance

1. What are some of the most common types of HIV drug resistance in your country? What are the trends/patterns of HIV drug resistance in your country? Why and how did that develop?
2. What are the factors (individual level and system level) that cause and perpetuate HIV drug resistance in your country?
3. What are the impacts of HIV drug resistance in your country?
4. What are the existing policy strategies or interventions implemented to address HIV drug resistance in your country, if any? Are there any considerations behind deciding to implement these strategies/interventions, if any?

B. Policy Implications: Opportunities, Challenges, Financial Implications, Financing Instruments

1. What are some of the opportunities and challenges involved in addressing HIVDR in your country?
2. What are the key challenges for PLHIV to access HIV services in your country?
3. What are your suggestions/recommendations in improving HIV treatment and HIV related service access to people living with HIV (PLHIV) in your country?

Table S1 Participant characteristics (n=17)

Participant No	Country	Role in HIV response
IDI17	Brunei	Government
IDI05	Cambodia	Non-governmental organisation
IDI06	Cambodia	Researcher
IDI08	Cambodia	Government
IDI04	Indonesia	Researcher
IDI09	Indonesia	Researcher, non-governmental organisation
IDI07	Lao People's Democratic Republic	Researcher
IDI01	Malaysia	Non-governmental organisation
IDI13	Malaysia	Researcher
IDI12	Myanmar	Non-governmental organisation
IDI14	Myanmar	Non-governmental organisation
IDI11	Philippines	Nurse, consultant
IDI16	Philippines	Non-governmental organisation
IDI15	Singapore	Infectious disease physician, government
IDI02	Thailand	Infectious disease physician, researcher
IDI10	Thailand	Infectious disease physician, researcher
IDI03	Timor Leste	Infectious disease physician, non-governmental organisation

HIV, human immunodeficiency virus.