Vietnam Administration of HIV/AIDS Control, Ministry of Health
National Hospital for Tropical Diseases
AIDS Clinical Center, National Center for Global Health and Medicine

HIV Drug Resistance Knowledge Book

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Abbreviations

3TC	Lamivudine
ABC	Abacavir
AFB	Acid-fast bacillus
AIDS	Acquired immunodeficiency syndrome - Hội chứng suy giảm miễn dịch mắc phải
ALT	Alanine aminotransferase
ARV	Antiretroviral
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
CD4	T-lymphocyte bearing CD4 receptor
DNA	Desoxyribonucleic acid
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir
EFV	Efavirenz
FTC	Emtricitabine
HBs Ag	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
INSTI	Integrase strand transfer inhibitor – Thuốc ức chế men tich hợp
LPV/r	Lopinavir/ritonavir
NNRTI	Non-nucleoside reverse transcriptase inhibitor - Thuốc ức chế men sao chép ngoợc non - nucleoside
NRTI	Nucleoside reverse transcriptase inhibitor - Thuốc ức chế men sao chép ngoợc nucleoside
NVP	Nevirapine
PrEP	Pre-exposure prophylaxis - Dự phòng troớc phơi nhiễm
RNA	Ribonucleic acid
RAL	Raltegravir
PI	Protease inhibitor - Thuốc ức chế men protease
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organization

Preface

Vietnam has made substantial progress in controlling the HIV epidemic and expanding access to antiretroviral therapy (ART). The number of new HIV infections was 2,700 in 2021; this number peaked in the early 2000s and has continued to decline over the years. It was estimated that 240,000 people were living with HIV at the end of 2021, for all of whom the access to ART is secured by national policies.

Despite this, Vietnam faces a new challenge in the transition of the financing system of HIV treatment services. International partners have gradually shifted their financial support to technical assistance in accordance with the country's economic growth, and the country has expanded the social health insurance (SHI) coverage for HIV treatment services. Antiretroviral (ARV) drugs have been provided free of charge by international programs, but the SHI system requires out-of-pocket payment and the de-centralization of services. In this situation, disengagement from care and suboptimal adherence to treatment may occur, and leads to increased risk of the emergence and transmission of drug-resistant HIV. Furthermore, pre-exposure prophylaxis (PrEP) was introduced in 2018 in Vietnam, and HIV drug resistance (HIVDR) could be another challenge in terms of PrEP efficacy.

In this context, a research project based on a request from the Government of Vietnam was started in 2019, entitled "Establishment of the 'bench-to-bedside' feedback system for sustainable antiretroviral therapy and the prevention of new HIV transmission in Vietnam," under the Science and Technology Research Partnership for Sustainable Development (SATREPS) funded by the Japan International Cooperation Agency (JICA) and Japan Agency for Medical Research and Development (AMED). The SATREPS in Vietnam is jointly implemented by the National Hospital for Tropical Diseases (NHTD), Hanoi Medical University, the Administration of HIV/AIDS Control (VAAC), the Ministry of Health of Vietnam, and the AIDS Clinical Center, National Center for Global Health and Medicine (ACC, NCGM), Japan. In this project, the NHTD and 10 regional ART clinics developed a network to monitor HIV viral load (VL) and HIVDR in people living with HIV (PLWH) who are on ART and in newly infected, ART-naïve patients. Also, the SATREPS project investigates the transmission of drug-resistant virus in those who are newly infected with HIV while on PrEP.

The SATREPS project has revealed prevalences of transmitted drug resistance (TDR) and acquired drug resistance (ADR) as low as 5.0% and 2.5%, respectively, as of March 2022. However, a certain number of PLWH have persistently high HIV VL or multi-class drug-

resistant HIV infection. In addition, one-third of PLWH with viremia who are on ART are infected with HIV strains that are still susceptible to their current ART regimen, requiring adherence support rather than regimen changes.

This knowledge book was developed under the leadership of the VAAC in collaboration with the SATREPS project and other national and international HIV experts. Through a series of discussions among these contributors regarding the SATREPS results described above, this knowledge book was designed as a guide for health care professionals to better manage patients with HIV viremia.

We hope that this knowledge book will help health care professionals in Vietnam to obtain essential knowledge and practical skills so as to contribute to prevention of the emergence and transmission of HIVDR for achievement of the 95-95-95 targets to end the HIV epidemic in Vietnam.

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Chapter 1. General Introduction

1. HIV drug resistance (HIVDR) worldwide and in Vietnam

HIVDR is caused by mutations in the viral gene that codes the target molecules of ARVs, which affects the ability of ARV drugs to block viral replication. All ARVs can become partially or fully ineffective with the emergence of drug resistance-associated mutations (DRMs), potentially leading to treatment failure and increased HIV-related morbidity and mortality. Additionally, the World Health Organization (WHO) recommends that oral PrEP be offered as an additional choice for HIV prevention. Access to PrEP is currently being expanded in over 30 provinces/cities in Vietnam. The ARV regimen used in PrEP is a two-drug regimen. PrEP is only effective for those without HIV infection. If an individual living with HIV initiates PrEP during the window period, the HIV test result is still non-reactive, which can lead to the emergence of drug-resistant HIV.

HIVDR can be classified according to the conditions under which DRMs occur, as follows.

- Acquired drug resistance (ADR): emergence of DRMs when HIV replicates during ART
- Transmitted drug resistance (TDR): infection with drug-resistant HIV
- Pretreatment HIV drug resistance (PDR): any DRM detected before ART. This includes TDR and acquired DRM with previous exposure to ARVs, including owing to prevention of mother-to-child transmission (PMTCT) or incomplete PrEP

The WHO recommends periodic HIVDR surveillance so as to decide appropriate changes in treatment strategies.

Owing to the scale-up of ART globally over the past decade, the level of drug resistance has steadily increased in recent years. According to national representative surveys on HIVDR, 21 out of 30 countries have reported that the prevalence of PDR to nevirapine (NVP) or efavirenz (EFV) among those who initiate first-line regimen is more than 10%; high levels of ADR to these ARVs among individuals with treatment failure are also observed [1]. Given these findings, the WHO recommends accelerating the transition to dolutegravir (DTG)-based ART [1]. In contrast, the surveys showed that PrEP-associated resistance is infrequent, with only a few individuals who seroconvert while taking PrEP [1].

Vietnam has a high viral suppression rate, at 96.0% in 2020 [1]. Additionally, Vietnam has achieved the 2025 UNAIDS target of >95% VL suppression. The prevalence of ADR and PDR is also low. By 2022, Vietnam had conducted three national HIVDR surveys. The prevalence of any ADR was 3.0% at ≥12 months [3], 4.6% at ≥36 months (2013) [2], and 3.4% at ≥48 months (2017) after ART initiation [3]. The prevalence of PDR in 2017 was 5.8% [3]. However, Vietnam is facing a variety of unique challenges that could lead to an increase in HIVDR, including an increase in HIV infections among

men who have sex with men [4], rapid expansion of PrEP use [5], and a transition to HIV services under the SHI system [6]. To maintain the achievements to date, it is important to continue monitoring HIVDR and to ensure the effectiveness of ART.

2. Scope of the knowledge book

VL testing, treatment adherence, and HIV drug-resistance testing during ART among PLWH have been recommended by the Ministry of Health in the Guidelines for HIV/AIDS Treatment and Care. However, there are currently no systematic documents regarding these contents that support clinical practice among medical staff. Therefore, the SATREPS Project has coordinated with VAAC and the National Hospital for Tropical Diseases to develop this knowledge book.

The SATREPS project considers that two types of capacities need to be strengthened among HIV health care professionals in Vietnam to promote the prevention and treatment of drug-resistant HIV:
1) Understanding the needs and indications for VL monitoring as well as HIVDR testing and the interpretation of test results.

2) Providing comprehensive adherence support using an individualized approach.

Goals: By referring to the knowledge book, readers will be able to 1) understand the principals of VL monitoring, HIVDR testing, and adherence support, and 2) interpret the results of testing for VL and common DRMs in Vietnam.

Target readers: Health care professionals caring for PLWH (e.g., medical doctors, nurses, public health experts, and counselors) at all health care facility levels in Vietnam.

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Chapter 2. Monitoring during ART

1. ART treatment monitoring

ART monitoring is carried out according to the Guidelines for HIV/AIDS Treatment and Care issued by the Ministry of Health in Decision No. 5968/QD-BYT, dated December 31, 2021.

1.1. Within the first 6 months after ART

Mortality among PLWH on ART is usually highest in the first 3 months after ART initiation [1], especially in those with advanced HIV disease, co-infection and/or comorbidities, severe anemia, cachexia, or malnutrition. The following practices should be carried out. [2]

- Monitoring clinical symptoms
- Managing opportunistic infections (OIs), including immune reconstitution inflammatory syndrome (IRIS)
- Assessing and managing side effects and drug–drug interactions
- Assessing and supporting adherence to ART

1.2. After 6 months post-ART initiation

The response to ART should be evaluated to identify patients who are not virally suppressed and require support. The following evaluation should be completed.

- Clinical response: physical examination or symptom evaluation for clinical staging (see Appendix 1.) including weight, adverse drug reactions, adherence to ART, new or recurrent OIs, IRIS, and pregnancy status in women and adolescent girls of childbearing age
- Immunologic response: regular CD4 count test
- Virologic response: regular VL and HIVDR testing when indicated

2. Monitoring of treatment adherence

2.1. Definition of treatment adherence

Treatment adherence is the degree to which a patient engages in health behaviors with respect to taking medicines as indicated (right drug, right dose, right method, right route, and right time), attending regular clinic visits, and receiving laboratory testing as recommended [2]. The reported level of ART adherence needed to achieve viral suppression is ≥95%. Poor adherence may lead to viral replication and subsequent development of ADR and increase the risk of HIV transmission as well as morbidity and mortality owing to disease progression.

2.2. Assessment of treatment adherence

Early recognition of suboptimal adherence is crucial for early intervention, and adherence should be monitored at every follow-up visit [2]. Methods of assessment include counting the remaining drugs, self-reporting by the patient, use of a self-recording booklet, supporters' report, or VL test results. Other indicators of suboptimal adherence include missing clinic appointments, irregular clinic visits, or having symptoms of psychological or neurocognitive disorders [2,3].

3. HIV viral load (VL) monitoring

VL measurement using real-time PCR (copies/mL) is the gold standard for identifying treatment failure and patients who require improved adherence support [4] and genotypic HIVDR testing. The following schedule of VL monitoring is recommended. [2]

- At 6 months and 12 months after ART initiation, re-starting ARV, treatment failure, and every 12 months thereafter
- When treatment failure is suspected
- At 34–36 weeks of pregnancy and every 6 months while breastfeeding to assess the risk of vertical HIV transmission and determine the PMTCT regimen for the baby

4. Evaluation of VL results and treatment

ART is considered effective when the VL is below the suppression threshold, especially when testing shows a VL of less than 50 copies/mL. With a VL below 200 copies/mL, PLWH will not transmit HIV to their sexual partners. When the VL falls below 50 copies/mL, the rate of HIV transmission from mother to child drops to less than 0.5% [5,6]. In 2023, the WHO stated that PLWH who are on ART and have a VL of less than 1000 copies/mL have near zero or minimal risk of transmitting HIV to their sexual partners.

The flow of VL-guided care is shown in Figure 1 [2]. If VL is over 50 copies/mL, adherence counseling and confirming the presence of any factors that could affect blood concentrations of ARV (e.g., DDI, decreased absorption) are recommended. Then, VL testing should be repeated after 3 months. If the result of VL testing is >1000 copies/mL at two consecutive time points 3 months apart, HIVDR testing and switching to a second-line regimen should be considered, if available.

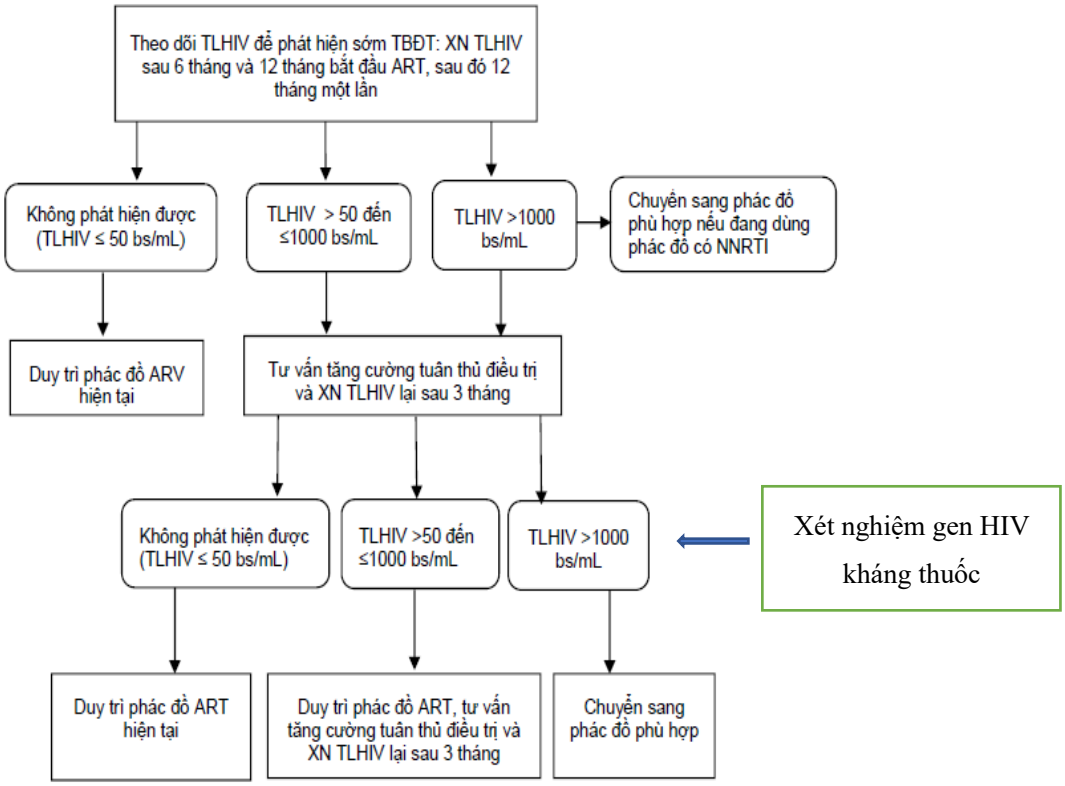

Figure 1 Antiretroviral therapy (ART) and treatment failure

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Chapter 3. HIV drug resistance

1. General mechanism of HIV drug resistance (HIVDR) and HIV drug-resistant forms

HIVDR is defined as the presence of mutations[1] in the gene that codes the target molecules of ARVs and affect the ability of ARVs to block viral replication. HIV lacks the ability to correct transcription errors when replicating its genome and frequently yields strains with mutations. HIV replicates very rapidly, producing 10^9 (10 billion) virions[2] per day in one individual [1,2]. All of these characteristics are attributable to a mode of viral population structure, called quasispecies, in which collections of closely related genomes exist in a continuous process of genetic variation, competition, and selection in a host. Under the incomplete pressure of ART, the selection of resistant HIV can emerge and DRMs can further accumulate as the failing ART regimen is continued, leading to wider cross-resistance to other ARVs in the same class. In the absence of ARVs, most resistant HIV strains will have less replication capacity than wild-type[3] HIV, and resistant HIV is quickly replaced by wild-type HIV. Therefore, drug-resistance testing should be performed and interpreted in consideration of these characteristics.

2. Indications for drug resistance testing

HIVDR testing aims to detect archived resistance mutations in an individual, which can be used to determine effective ART regimens and prevent unnecessary changes in the ART regimen. It is critical to avoid the accumulation of DRMs and preserve effective ARV options for future treatment. The longer a failing regimen is maintained, the more likely multiple cross-resistance mutations will accumulate, causing high-level and multidrug resistance. Early detection of treatment failure and timely changes in the appropriate regimen are very important.

HIVDR testing is generally recommended for those on ART but who are not being virally suppressed, suspected as having treatment failure, or those with suboptimal adherence. In the guideline, HIVDR testing is recommended with VL >1000 copies/mL at two consecutive time points 3 months apart and before switching ART regimens [3].

Because strains with DRMs are likely to be replaced by wild-type HIV within 4–6 weeks in the absence of drug pressure, HIVDR testing is usually recommended before or immediately after drug discontinuation. DRMs may disappear without the selection pressure of ARVs, and the mutations

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[1] Mutation is a change in the genetic sequence of an organism and is the cause of diversity among organisms. Changes can occur at different levels and have different consequences such as reducing the organism's resistance to drugs, or increasing or decreasing virulence or infectivity.

[2] A virion is a fully assembled virus particle consisting of an outer protein shell (capsid) with a nucleic acid core (genome), in addition to a number of other compounds, some with an outer shell (comprising lipid+protein); some may have additional glycoprotein spikes.

[3] A wild-type virus is a naturally occurring virus that does not mutate.

noted in previous tests may not be detected in the present test. However, all archived DRMs in previous HIVDR tests have clinically important implications and should be taken into consideration when choosing a second-line regimen. Although HIVDR testing is not performed before or immediately after the cessation of failing ART, HIVDR testing when restarting ART may still be useful and should be considered. Consultation with HIV experts and intensive adherence support are strongly recommended before the ART regimen is changed.

For those diagnosed with HIV infection while on PrEP, HIVDR testing is recommended before ART initiation. Because suboptimal adherence to PrEP can cause HIVDR, PrEP users should receive regular HIV testing and counseling to maintain adherence so as to avoid HIV acquisition and emergence of HIVDR.

3. Common drug resistance mutations (DRMs)

Over 200 mutations are associated with drug resistance among six classes of ARV drugs worldwide [4], of which four drug classes are currently available in Vietnam: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitor (PIs), and integrase strand transfer inhibitor (INSTIs). DRMs are classified according to the mechanism of emergence, as follows: 1) major mutations that are predominantly located in the active site of ARV, 2) accessory mutations that usually occur in combination with major mutations, and 3) polymorphic mutations that exist naturally and are subtype-dependent. Major mutations play a major role in reducing the susceptibility to ARVs.

The Stanford University HIV Drug Resistance Database (USA) is an essential, regularly updated database and the most commonly used HIV drug resistance databasein the world. With one or more gene sequences uploaded to the website (https://hivdb.stanford.edu/hivdb/by-sequences/), the database provides information on drug resistance mutations, resistance levels, important recommendations, and importance of the impact of the found mutation on ARV drugs. This database also allows users to enter specific mutation locations (https://hivdb.stanford.edu/hivdb/by-patterns/) to assess the level of drug resistance and consider related recommendations.

In addition, the International Antiviral Society–USA provides a list of mutations related to HIV drug resistance and very useful recommendations for physicians. This list of mutations is regularly updated on the website (https://www.iasusa.org/resources/hiv-drug-resistance-mutations/).

The tables below summarize the main resistance mutations to common ARV drugs in each class (NRTI, NNRTI, PI, and INSTI), including:

Bold and underline indicate mutations causing high levels of drug resistance

- **Mutations in bold** indicate mutations causing low to moderate levels of drug resistance
- (*) indicates mutations that can increase drug sensitivity

- Others can potentially reduce susceptibility when combined with other mutations

Mutations are described below [5,6].

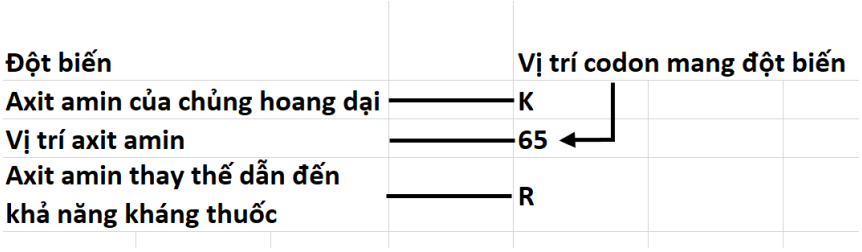

Figure 2. Description of the meaning of a mutation location [6].

3.1. Resistance mutations to nucleoside reverse transcriptase inhibitors (NRTIs)

	Non-TAMs					TAMs						MDR	
	184	**65**	**70**	**74**	**115**	**41**	**67**	**70**	**210**	**215**	**219**	**69**	**151**
Cons[4]	**M**	**K**	**K**	**L**	**Y**	**M**	**D**	**K**	**L**	**T**	**K**	**T**	**Q**
3TC	**VI**	R										**Ins**	**M**
FTC	**VI**	R										**Ins**	**M**
ABC	VI	**R**	E	**VI**	**F**	L			W	FY		**Ins**	**M**
TDF	***	**R**	E		F	L		R	W	FY		**Ins**	**M**
AZT	**	**		*		**L**	**N**	**R**	**W**	**FY**	QE	**Ins**	**M**

Table 1 *Common major resistance mutations to NRTIs [5]*

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; TAM, thymidine analog mutation; MDR, multidrug resistance; 3TC, lamivudine; FTC, emtricitabine; ABC, abacavir; TDF, tenofovir disoproxil fumarate; AZT, zidovudine.

M184V/I: Despite causing high resistance to lamivudine (3TC)/FTC and low/moderate resistance to abacavir (ABC), M184V/I increases susceptibility to TDF and zidovudine (AZT) and reduces viral replication. It is reasonable that 3TC/FTC can be still used in those with this mutation.

K65R is the most common DRM in TDF, with a 2-fold change but increased susceptibility to AZT. The combination of K65R+M184V/I reduces TDF susceptibility less than 1.5-fold. Those with K65R+M184VI will respond well to TDF/3TC with a highly potent third drug (e.g., DTG,

[4] Cons (consensus amino acid): the most common amino acid at a codon position in a specific gene region, which may be specific to one or more types. For example, at codon 184 in the reverse transcriptase gene region, the most common amino acid for all HIV-1 types is methionine.

lopinavir/ritonavir [LPV/r]) or better than those receiving AZT/3TC, even though K65R increases AZT susceptibility.

TAMs (thymidine analog mutations) occur under the pressure of thymidine analogues, such as AZT. T215Y/F causes moderate/high resistance to AZT. T215S/C/D/E/I/V/A/L/N (T215 revertant) usually occurs from viruses containing T215Y/F, which does not reduce susceptibility to NRTIs. The occurrence of these mutations may indicate that the patient has been infected with viruses carrying T215Y/F.

MDR (multidrug resistance): T69Ins often co-occurs with TAMs during prolonged use of failing NRTI-containing regimens, resulting in moderate resistance to 3TC and FTC, and high resistance to AZT, ABC, and TDF. Q151M accumulates with non-TAMs when combined with at least two of minor mutations such as A62V, V75I, F77L, and F116Y and confers high resistance to AZT and ABC, as well as moderate resistance to TDF, 3TC, and FTC.

3.2. Resistance mutations to non-nucleoside reverse transcriptase inhibitors (NNRTIs)

	100	**101**	**103**	**106**	**181**	**188**	**190**	**227**	**230**
Cons	**L**	**K**	**K**	**V**	**Y**	**Y**	**G**	**F**	**M**
EFV	**I**	E**P**	**NS**	**AM**	CIV	**L**	**ASE**	L**C**	**L**
NVP	**I**	**EP**	**NS**	**AM**	**CIV**	**L**	**ASE**	**LC**	**L**

Table 2 Common major resistance mutations to NNRTIs [5]

Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitor; EFV, efavirenz; NVP, nevirapine.

Major mutations: NNRTIs have a low genetic barrier to resistance[5], meaning that the development of just one major mutation leads to drug resistance. The major mutations shown in Table 2 often cause cross-resistance with most drugs in this class.

Minor mutations: Y188C/H leads to moderate/high EFV resistance. G190Q is rare but may have the same effect as G190E. P225H is often selected under the pressure of EFV and occurs together with K103N. The combination of V179D+K103R reduces susceptibility to NVP and EFV more than 10-fold.

[5] Genetic barrier to resistance: the number of accumulated mutations needed to cause drug resistance.

3.3. Resistance mutations to protease inhibitors (PIs)

	32	46	47	48	50	54	76	82	84	88	90
Cons	**V**	**M**	**I**	**G**	**I**	**I**	**L**	**V**	**I**	**N**	**L**
ATV/r	**I**	IL	V	**VM**	**L**	VTALM		ATFS	**V**	**S**	**M**
DRV/r	**I**		VA		**V**	**LM**	**V**	F	**V**		
LPV/r	**I**	IL	V**A**	VM	**V**	**VTALM**	**V**	**AFTS**	**V**		M

Table 3 Main resistance mutations to PI drugs [5]

Abbreviations: PI, protease inhibitor; ATV, atazanavir; DRV, darunavir; LPV, lopinavir; r, ritonavir.

Studies have demonstrated that LPV/r and darunavir/ritonavir (DRV/r) have high genetic barriers to resistance, which develops more slowly than resistance to NRTIs and NNRTIs. For resistance to develop, many mutations must accumulate in the protease gene region and/or on the adjacent gene region, such as Gag[6]. ATV/r has lower barriers to drug resistance.

Major mutations: I50L and N88S are the two main mutations that cause high resistance to ATV only. These increase the susceptibility to some other drugs, such as DRV/r in the presence of I50L or N88S and LPV/r in the presence of I50L.

Minor mutations: L10F, V11I, K20TV, L23I, L33F, K43T, F53L, Q58E, A71IL, G73STCA, T74P, N83D, and L89V/T are common nonpolymorphic accessory resistance mutations. The co-occurrence of three to five minor mutations may reduce drug susceptibility.

3.4. Resistance mutations to integrase strand transfer inhibitors (INSTIs)

	66	92	118	138	140	143	148	155	263
Cons	**T**	**E**	**G**	**E**	**G**	**Y**	**Q**	**N**	**R**
BIC	K	Q	**R**	KAT	SAC		**HRK**	H	**K**
CAB	K	Q	**R**	KAT	SAC**R**		**HRK**	**H**	**K**
DTG	K	Q	**R**	KAT	SAC		**HRK**	H	**K**
RAL	AI**K**	**Q**	**R**	**KAT**	**SAC**	**RCH**	**HRK**	**H**	K

Table 4 Main resistance mutations to INSTI drugs [5]

Abbreviations: INSTI, integrase strand transfer inhibitor; BIC, bictegravir; CAB, cabotegravir; DTG,

[6] Gag (group specific antigen) is a structural gene of the HIV virus that encodes outer core membrane proteins, capsid proteins, nucleocapsids, and a smaller nucleic acid stabilizing protein.

dolutegravir; RAL, raltegravir.

G118R and Q148H/R/K: These lead to multidrug resistance and high levels of resistance to most INSTIs.

Mutation complexes: Primary mutations, especially Q148H/R/K, can occur in combination with other primary mutations or several secondary mutations such as Q148H/R/K+G140S/A +/- G149A or N155H+E92Q. These increase the risk of drug resistance and virological failure.

Minor mutations: L74M, V151I, E157Q, G163KR, and D232N are common polymorphic accessory DRMs. The presence of L74M and T97A is between 1% and 5%, depending on subtype, among those who have not been treated with INSTIs and leads to reduced susceptibility to DTG and bictegravir (BIC) in combination with Q148H/R/K+(E138K±G140S/A). H51Y, F121Y, S147G, S153YF, and S230R are minor mutations that can accumulate under the selective pressure of all INSTIs.

DTG and BIC have a higher genetic barrier than raltegravir (RAL) and require the accumulation of DRMs to cause drug resistance.

4. Scoring the degree of drug resistance

Each mutation has a different impact on drug resistance. The degree of resistance of each mutation to a specific drug is expressed as a score, called the "drug penalty score." If the mutation increases the susceptibility to a certain drug, the penalty score is negative. The total penalty score of the regimen represents the level of resistance to the regimen and may be useful in decision-making regarding a regimen change. Drug resistance is often divided into five levels corresponding to the total penalty score mentioned above.

Penalty score	Resistance level	Meaning
0–9	Sensitive	There is no evidence of decreased drug susceptibility.
10–14	Potentially low-level resistance	The virus is not yet resistant but has mutations that can cause resistance when other DRMs are further accumulated.
15–29	Low-level resistance	The virus has DRMs that possibly decrease the response to ART.
30–59	Moderate resistance	The virus has DRMs that reduce drug susceptibility.
≥60	High-level resistance	The virus has DRMs that cause high-level resistance.

	ABC	AZT	FTC	3TC	TDF
K65R	45	-10	30	30	50
D67N	5	15	0	0	5
M184V	15	-10	60	60	-10
Total	**65**	**-5**	**90**	**90**	**45**

Table 5 An example of an NRTI resistance score table. Although accumulation of the mutations M184V and K65R confers high resistance to 3TC, these increase susceptibility to AZT (negative penalty score). Therefore, maintaining a regimen with 3TC and AZT may still be effective.

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; 3TC, lamivudine; AZT, zidovudine; ABC, abacavir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

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Chapter 4. Adherence support

Maintaining optimal adherence to ART is essential to ensure the efficacy of ART [1]. Non-adherence is by far the most likely cause of viral non-suppression rather than drug resistance. Key components of adherence counseling include obtaining informed consent, addressing challenges and barriers to adherence, and discussing how to manage these with a multi-disciplinary team before and during ART [2].

1. Providing information and consent from patients regarding ART

Before initiating ART, the patient should have a good understanding of HIV infection and be informed the benefits and risks of ART and the importance of continuing treatment [4,5] in a plain-language format that patients can easily understand. Information and ART adherence support should be provided by a multi-disciplinary team that includes doctors, nurses, counselors, and treatment supporters. Each member should provide information based on their own expertise, but the information should be consistent and appropriate.

Of note, PLWH who are informed about Undetectable=Untransmittable by a health care professional have significantly better health outcomes than those who are not informed [6]. Patients should also be given the opportunity to ask questions and to discuss their concerns with health care professionals. It is important to confirm that patients understand the information provided according to the viewpoint of different professionals, such as doctors and nurses.

2. Individualized adherence assessment

Challenges and barriers that may affect ART adherence and how the patient perceives and tries to cope with these should be discussed. In this process, health care professionals should build a trusting relationship with the patient, listen to the patient, and understand the patient's perception or narrative regarding the situation or reason for optimal or suboptimal adherence.

Patient information should be collected from various perspectives. The "Consultant sheet enhances treatment adherence" (see Appendix. 2) [7] may be useful for collecting comprehensive information. This sheet permits evaluation of factors affecting adherence in terms of four aspects: behavioral factors, health factors and awareness, economic and social factors, and emotional and mental factors. This tool can also help in developing a plan to increase adherence. In addition to these factors, side effects should be assessed after ART initiation.

The medication schedule should be considered based on each patient's lifestyle. When creating a timetable of the patient's daily activities, discussion is useful to identify what time is the most

convenient to take medicines. Specifying how and where to store medicines and how to prevent or rescue missed doses, such as with use of a calendar or a mobile application [8], are also encouraged before initiating ART.

3. Finding resources and support

Support from family and friends may help patients to maintain good adherence [1]. It is important to hold discussions to determine who knows the patient's HIV status and who might be able to support the patient. Disclosing HIV status to possible supporters is always a big challenge and must not be forced. Patients should be informed when, how, and to whom their HIV status should be disclosed as well as that it is the patient's choice and that health care professionals can help in the process of disclosure. Additionally, if patients have difficulty getting support from family and friends or are facing problems such as drug addiction, it is important to help them find appropriate support, such as in peer groups or harm reduction centers.

4. Active involvement of the patient

It is important for health care professionals to encourage patients to make decisions by themselves, which leads to their proactive engagement in care and behavior modification [3,9]. The following interview techniques may be useful to encourage behavioral changes.

- Cognitive behavioral therapy (CBT) [10-12]

CBT is a type of psychotherapy that works on "cognition," such as how to perceive reality and how to see things, to help create well-balanced and adaptive thoughts. CBT is an effective method of behavior modification and is applied to change self-management in patients with chronic diseases.

- Motivational interviewing (MI) [13-15]

MI is a counseling approach that draws out and respects the patient's autonomy, finding the direction in which the patient wants to change, and supporting the patient in trying to change. The principles of MI include expressing empathy, developing awareness about discrepancies between behavior and the desired change, avoiding argumentation, rolling with resistance, and supporting self-efficacy.

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Chapter 5. Case studies

Case 1: Adult patient infected with HIV through mother-to-child transmission

Case presentation:

A male in his 20s who was diagnosed with HIV infection at birth; his mother was found to be HIV positive shortly before his birth. He began ART with d4T/3TC/NVP at the age of 7 years and was later switched to TDF/3TC/EFV, upon which he became stable, with undetectable VL. At age 18 years, the patient was transitioned from the pediatric department to the adult HIV clinic. Irregular visits and poor adherence were noted from 6 months after the transition. Now, he presents with a cough and oral candidiasis. His CD4 count is 57 cells/μL and HIV-RNA is 413,000 copies/mL. The patient was referred for HIV drug-resistance testing but no drug resistance mutations were detected. High VL continues to be detected; however, he denies missing his medication. He does not have any other history of illness and no history of drinking, smoking, or illegal drug use. The patient has a part-time job. He does not live with his mother; he lives with his grandmother, who is very supportive. The patient states that his other relatives have a prejudice against people living with HIV.

Q. What should be done first in considering the factors that influence treatment adherence?

A. Check whether the patient has had side effects from ART and whether taking the medication causes physical distress. If oral administration is not possible owing to side effects, changing the ART regimen should be considered. It is important to listen attentively to the patient so as to get to know him.

Q. It seems that the patient did not honestly report that he forgot to take his ARVs. How would you approach him?

A. The patient was infected with HIV through mother-to-child transmission and was diagnosed with HIV infection in early childhood. Therefore, he has been taking ARVs for a long time. First, offer the patient support and empathy, acknowledging his need to use long-term medication and the fact that he is living with HIV [1-3]. Then, ask the patient about his knowledge and understanding of HIV infection, his living conditions and relationships, and his thoughts and feelings about being infected with HIV. If it is found that the patient lacks knowledge or is unable to accept having HIV infection, provide the patient with education and psychological care and coordinate support for individualized care.

Q. It is found that the patient has negative feelings about HIV infection because he is stigmatized by his relatives and other people owing to HIV infection. How would you support this patient?

A. The painful feelings when a person is stigmatized by others do not go away easily. In particular, stigma from close relatives can leave deep scars in the hearts of affected patients. First, listen to the feelings and thoughts that the patient has been facing. As a health care professional, share your understanding with the patient to build a trusting relationship. Then, to promote cognitive transformation such that the patient is less affected by others' prejudice against HIV infection, encourage him to turn to those people who are currently supportive [4-6]. The patient should receive ongoing support in consultation over time to help him view his life more positively.

Summary:

To support treatment adherence, it is important to understand the patient's true thoughts and feelings. As a multidisciplinary team, it is also important to comprehensively assess and empathize with the patient through the information that they share, such as regarding their living situation and relationships. Health care professionals should understand the patient's surrounding environment, thoughts, and ideas to best empathize with and support the patient. It is essential for the multidisciplinary team to follow a standard policy and work together with patients to support cognitive and behavioral changes.

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Case 2: Multiclass drug resistance: evolution of resistance during a regimen containing LPV/r

Case presentation:

A 40-year-old male was diagnosed with HIV infection 5 years earlier and started ART with TDF/3TC/EFV. Two years after the initial regimen, his VL increased owing to poor adherence. HIVDR testing revealed a K103N and a M184V mutation, which led to a switch from EFV to LPV/r. Despite an initial good response to TDF/3TC/LPV/r, his clinic visits were interrupted for financial reasons. When the patient was seen again, his VL was still high although he was advised to improve adherence. The development of a V82A mutation in the protease region associated with LPV/r resistance was identified.

Viral Load	**10000 copies/mL**
NRTI mutation	M184V
NRTI resistance	ABC: Low-level Resistance AZT: Susceptible FTC: High-level Resistance 3TC: High-level Resistance TDF: Susceptible
NNRTI mutation	K103N
NNRTI resistance	EFV: High-level Resistance NVP: High-level Resistance
PI mutation	V82A
PI resistance	LPV/r: Intermediate Resistance

Table 6 Results of HIV drug-resistance testing at the time of re-engagement with care.

Q. How would you manage this case based on the drug resistance results?

A. HIVDR testing showed that the patient had developed multiclass drug resistance while receiving TDF/3TC/EFV and TDF/3TC/LPV/r. The K103N mutation confers resistance to NNRTIs such as EFV. The V82A mutation causes resistance to some PIs, including LPV/r (see Chapter 3: HIV drug resistance). The M184V mutation confers high-level resistance to 3TC but increases susceptibility to TDF and is considered to decrease the capacity of a virus to produce an infectious copy. Although the V82A mutation causes intermediate resistance to LPV/r, the patient can still continue the current treatment regimen. However, considering availability and accessibility in Vietnam, one option for the third regimen is TDF/3TC/DTG, replacing LPV/r with DTG, an INSTI that is not affected by the

mutations above. Of note, even with M184V, the regimen still contains two effective drugs, and M184V has some extra benefits, as described earlier. Identifying and removing barriers to the patient visiting a clinic is also crucial before switching to TDF/3TC/DTG.

Summary:

This case illustrates the challenges faced by a patient who developed triple-class drug resistance during therapy with LPV/r. Understanding the unique characteristics of each resistance mutation can lead to optimal selection of the next regimen.

Case 3: Patient with tuberculosis (TB) infection and drug resistance mutation

Case presentation:

This case involves a female patient born in the 1970s who began receiving ART at an outpatient clinic in 2019. She was diagnosed with HIV infection in 2014 at a prison and was treated with TDF/3TC/EFV. She was released from prison in 2018 and discontinued ART until 2019. Her husband died with unknown HIV status. She has three children, and they all are HIV negative. When she restarted ART, her body weight was 39 kg and she had anemia. Her hemoglobin level was 80 g/L and her CD4 count was 6 cells/μL. The patient reported that she took her medication without missing any doses. However, she lost 4 kg of body weight in 6 months. VL was 217,000 copies/mL in 2020. HIVDR testing showed the following mutations: K103N, V108I, G190A, V75VM, L74V, and M184V.

Q. How should these drug resistance mutations be interpreted? What is the best ART regimen for the patient?

A.

The table below describe the resistance level of each drug:

NRTI mutation	L74V, V75VM, M184V
NRTI resistance	ABC: High-level Resistance AZT: Susceptible FTC: High-level Resistance 3TC: High-level Resistance TDF: Susceptible
NNRTI mutation	K103N, V108I, G190A
NNRTI resistance	EFV: High-level Resistance NVP: High-level Resistance

NNRTI resistance mutations, such as K103N, V108I, and G190A, confer high-level resistance to EFV and NVP. Therefore, these ARVs will not be effective if they are continued.

NRTI resistance mutations show that only M184V causes high-level resistance to 3TC; however, this mutation reduces the virus' ability to replicate (see Chapter 3) and increases sensitivity to TDF. Therefore, maintaining a regimen with TDF and 3TC will still be effective in inhibiting virus replication.

No resistance was found to PIs (i.e., LPV/r) or to INSTIs (i.e., DTG). Therefore, the following

regimens would be effective: TDF/3TC/DTG or TDF/3TC/LPV/r. The TDF/3TC/DTG (TLD) regimen is best because of its high virus suppression effect.

Q. How would you advise this patient? How should the ART regimen be changed?

A. Considering the patient's history and drug resistance results, she may have a problem with treatment adherence. It is necessary to identify the reasons for poor adherence, specifically regarding the following.

- Having an inadequate understanding of HIV and ART
- Side effects of the TDF/3TC/EFV regimen (e.g., insomnia, depression owing to EFV)
- Social and psychological problems (e.g., work, accommodation/housing, stigma, discrimination)

Consultation with the patient should be also provided, focusing on the following issues:

- The patient has had both virological and clinical failure, which involves a high risk of morbidity and mortality.
- The new regimen (TDF/3TC/DTG) is highly effective against HIV in this patient. She must fully comply with taking the medication (1 tablet per day, at a specific time). It is important to discuss support and medication reminders with this patient.
- Provide decision support to enable the patient to be proactive in her treatment and make positive behavioral changes. It may also be useful to relate stability in the patient's own life to maintaining stability in her treatment so that it can be visualized. For example, when the patient's physical condition is stable, she is able to care for her family and children.

Subsequent developments: After switching to the TDF/3TC/DTG regimen for 3 weeks, the patient developed a mild fever and cough, with blood-stained sputum. The sputum test results were as follows: acid-fast bacillus test 3+, Xpert MTB+, no resistance to rifampicin or isoniazid (RH). The patient was diagnosed with pulmonary TB and was assigned TB treatment with the first-line regimen including rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E), i.e., 2RHZE/4RHE.

Q. Does the ART regimen need to be adjusted during TB treatment in this patient?

A.

- Adjustment needed.
- Adjustment plan:

1) If single-dose DTG 50 mg tablets are available: continue the TLD regimen, and increase the dose of DTG. Specifically, TDF/3TC/DTG 300/150/50 mg + DTG 50 mg (take 1 tablet of TLD and 1

tablet of DTG 50 mg).
2) If TLD single-dose tablets are not available, switch to a TDF/3TC/LPV/r regimen with a double dose of LPV/r.
Currently, single-dose DTG 50 mg tablets are available in Vietnam, so patients will continue to use the TLD regimen and take additional DTG 50 mg.

Subsequent developments: This patient was switched to a TDF/3TC/LPV/r regimen with a double dose of LPV/r because there was no single-dose DTG tablet available to continue the TLD regimen. She maintained good treatment adherence with both anti-TB drugs and ARVs. Her mother would remind her to take her medicines. She took the TB medicine right after waking up, and she set a phone alarm to remind her to take the ARVs twice a day. The patient gained weight, reaching 45 kg after 3 months of TB treatment. The results of VL testing after 6 months showed 23 copies/mL. She completed TB treatment 1 month after the VL test.

Q. How should the patient continue to be treated?

A. The patient should be informed about the importance of her VL test results and the clinical progression of both TB and HIV. Also, it should be emphasized that to have achieved such a good outcome, she must have complied well with both TB treatment and ART. After finishing TB treatment with rifampicin, the regimen can be returned to TLD because it is the most effective and a single-tablet regimen, which is better for adherence. Monitoring of treatment adherence and advice regarding appropriate adherence should be continued.

Summary:
This case demonstrates the risk of HIVDR related to poor ART adherence, especially among patients with life changes, e.g., being in or released from prison or family instability. This case also highlights the risk of HIV disease progression and death owing to HIVDR, with deterioration of CD4 cell counts and the development of OIs— with TB being the most common OI in Vietnam. HIVDR genotyping is helpful in choosing a subsequent ARV regimen. In the care of patients with HIV, special attention should be paid to DDIs between ARVs and other medicines the patient is taking, with the anti-TB drug rifampicin (R) being the most powerful inducer of DDIs. With the appropriate ART regimen and good treatment adherence support, the patient can do well in treatment for both HIV and TB with improved viral suppression and physical condition.

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Case 4: Renal dysfunction with the M184V mutation

Case presentation:

A 65-year-old male was diagnosed with HIV infection 10 years earlier and started on ART consisting of ABC, 3TC, and EFV. The patient initially responded well to the treatment, but his poor adherence led to suboptimal control of the HIV infection and emergence of the M184V mutation, which confers resistance to ABC and 3TC. Owing to the M184V mutation, the physician decided to change the patient's regimen to TDF/3TC/LPV/r. Although the changed regimen achieved an increase in his CD4+ T-cell count and a reduction in VL, regular monitoring revealed a decline in the patient's renal function, as demonstrated by increased serum creatinine levels and a decrease in creatinine clearance to 35 mL/min.

NRTI mutation	M184V
NRTI resistance	ABC: Low-level Resistance AZT: Susceptible FTC: High-level Resistance 3TC: High-level Resistance TDF: Susceptible

Q. How would you modify the patient's ART regimen considering his M184V mutation and renal dysfunction?

A. Given the decline in renal function, the physician should consider adjusting the patient's treatment regimen to minimize the potential nephrotoxic effects of TDF. Although ABC is often used in TDF-free regimens when TDF causes nephrotoxicity, the presence of the M184V mutation may render this approach ineffective. One option is to adjust the TDF dose according to renal function, as delineated below.

CrCl (mL/min)	**TDF dose**
>50	300 mg/24h
30-49	300 mg/48h
10-29	300 mg × 2 times/week
Dialysis	1 time/week or 12 hours after dialysis

Table 7 Adjustment of TDF dose according to renal function, from Ministry of Health guidelines. Particular attention should be paid to low body weight (less than 55 kg) as blood levels of TDF are higher and renal dysfunction is more likely.

Abbreviations: CrCl, creatinine clearance; TDF, tenofovir disoproxil fumarate.

Summary:

This case study highlights the challenges faced by an HIV patient who initially started treatment with ABC, 3TC, and EFV but developed the M184V mutation owing to poor adherence. The patient experienced renal dysfunction after switching to a regimen including TDF, 3TC, and LPV/r, necessitating further adjustments to his treatment plan.

Case 5: Initiation of ART in a patient with HIV infection after PrEP and M184V drug resistance mutation

Case presentation:

This case involves a male client, born in the 2000s, who enrolled in PrEP in 2020. In risk behavior assessment at the initiation of PrEP (Month 0), he reported that he had had unprotected sex with someone who was not his usual partner within the previous 1 week. He was prescribed 30 PrEP pills (TDF+FTC). The client returned to the clinic 36 days after receiving the medication at Month 0 and had used all 30 pills. He reported that he did not use any medication for 6 days and had not engaged in any risky sexual behavior between Month 0 and Month 1. HIV test results using the Alere combo test were reactive, with confirmatory test results showing that the client was HIV positive. He was referred for HIV treatment at the outpatient clinic at Hospital A. More than 1 month later, the results of HIVDR testing revealed the presence of the M184V mutation.

NRTI mutation	M184V
NRTI resistance	ABC: Low-level Resistance AZT: Susceptible FTC: High-level Resistance 3TC: High-level Resistance TDF: Susceptible

Q. How would you select the ART regimen for an HIV-infected individual who used PrEP with the TDF+FTC regimen and who has the M184V drug resistance mutation?

A. HIV-infected individuals should be examined, tested, and evaluated before treatment, like other PLWH, according to the Vietnam HIV-AIDS Treatment and Care Guidelines, as follows: screening for TB, sexually transmitted infections, co-infectious diseases, and noncommunicable diseases; CD4 testing, if possible; renal function tests; adherence counseling; and treatment planning. The client may have already been infected with HIV at the time of PrEP initiation (Month 1 might have fallen into the window period). Negative HIV test results were obtained within the window period, and acute HIV infection was overlooked at the initiation of PrEP. M184V causes high-level resistance to 3TC and FTC. However, it has been well noted that M184V reduces the capability for HIV replication, increases susceptibility to TDF, and reduces the risk of emergence of the K65R mutation, which causes resistance to TDF. Therefore, 3TC or FTC can be used with TDF if combined with a third drug, such as DTG. Considering that DTG has a high genetic barrier to resistance, TLD (TDF/3TC/DTG) is the preferred first ART regimen in individuals who were on PrEP but were infected with HIV. If TLD is

unavailable, TDF/3TC/EFV can also be used, but careful observation is required.

Summary: This case study highlights that the TLD regimen is the most appropriate for HIV-infected individuals who were on PrEP but acquired HIV infection and who have the M184V drug resistance mutation. Careful screening for acute HIV infection at PrEP initiation is required.

Case 6: Co- infection of HIV/hepatitis B virus

Case presentation:

A 30-year-old male was diagnosed with HIV infection and started ART with ABC, 3TC, and EFV. This regimen was initiated owing to signs of anemia and a high creatinine test result. The patient initially responded well to the treatment, but 3 months after ART initiation, his alanine aminotransferase (ALT) was elevated to 82U/L. The physician performed tests for increased liver enzymes, which were negative for both hepatitis C virus (HCV) antibody and rapid plasma reagin and positive for hepatitis B surface antigen (HBs-Ag). Because the screening test performed 6 weeks prior to the start of ART was negative for HBs-Ag, it was assumed that the patient was infected with hepatitis B virus (HBV) after the screening. HBV DNA was also detected at the time of ALT elevation. The patient's general condition was good and all other laboratory findings were normal.

Q. How would you modify the patient's ART regimen considering his HBV infection?

A. It is important to confirm the status of HBV infection prior to ART induction. Considering the potent efficacy and high genetic barrier against HBV of antiretroviral agents, a TDF-containing regimen (e.g., TDF/3TC/EFV or TDF/3TC/DTG) should be considered. Although 3TC also has anti-HBV activity, 3TC monotherapy against HBV often leads to the emergence of resistance to 3TC in HBV [1].

ARVs	Anti-HBV activity	Single use for HBV
TDF	✓	✓
3TC	✓	Not recommended

✓: yes

Table 8 ARVs with anti-HBV activity available in Vietnam

Abbreviations: HBV, hepatitis B virus; ARV, antiretroviral; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Summary:

This case highlights the need for HBV management with a TDF-containing ART regimen among HIV/HBV co-infected patients.

Robert G. et al. Lancet Infect Dis 2012 Apr;12(4):341-53.

Appendix 1. WHO clinical staging of HIV disease in adults and adolescents [a]

Clinical stage 1
Asymptomatic
Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruption
Fungal nail infections
Seborrhoeic dermatitis
Clinical stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than 1 month
Unexplained persistent fever (intermittent or constant for longer than 1 month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8g/dl), neutropaenia (<0.5 x 10^9/L) and/or chronic thrombocytopaenia (<50 x 10^9/L)
Clinical stage 4[b]
HIV wasting syndrome Pneumocystis (jirovecii) pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month in duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis, including meningitis

Disseminated nontuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)
Lymphoma (cerebral or B-cell non-Hodgkin)
Symptomatic HIV-associated nephropathy or cardiomyopathy
Recurrent septicaemia (including nontyphoidal Salmonella)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis

[a] In the development of this table, adolescents were defined as 15 years or older.

[b] Some additional specific conditions can be included in regional classifications, such as penicilliosis in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America.

Source: Adapted from: WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV related disease in adults and children. Geneva, World Health Organization, 2007

Appendix 2. Consultant sheet enhance treatment adherence

(For patients on ART with HIV> 200 copies / ml)

Full name: …….. **ID of patient record book: ……**

DOB: ……../……/…… **Sex: Female ☐ Male ☐**

Base information

Current ARV regiment: ……..…. 1st line ☐ 2nd line ☐

Latest VL test HIV results: …… Date of test:……/……/……

Adherence to treatment before counseling: Good (>95%) ☐ Not good (<95%) ☐

The 1st consultation to improve adherence:

Date: ……../……/……..With supporter for treatment participate: Yes ☐ No ☐

The factors that not adherence	Solutions to enhance adherence	Plan to increase adherence
Behavior factors ☐ Forger ☐ Damaging, losing drugs, giving drug ☐ Alcohol / drug use	**Interventions are carried out:** ☐ Individual consult on adherence ☐ Consult group on adherence ☐ There are support staff ☐ There are other patients supporting ☐ There is a support relative person ☐ Treatment of addiction / detoxification ☐ Other:	**Patients choose option to enhance adherence to treatment:** ☐ Ask relative person for support ☐ Get help from another patient ☐ Ask the support staff for reminders ☐ Treatment of addiction / detoxification ☐ Set alarm ☐ Set a reminder ☐ Use medicine dispensing box ☐ Reminder stickers on the wall ☐ Other: **When does implementation begin?** **Who support?**
Health factors, awareness ☐ Feeling healthy already ☐ Want to treat in other way ☐ Get sick ☐ Side effect		
Economic and social factors ☐ Traveling far, difficult ☐ Working far away ☐ No relatives supported ☐ Arrested (going to prison, rehab)		
Emotional, mental factors ☐ Boredom / depression / stress ☐ Guilt and fear of discrimination		

The 2nd consultation to improve adherence (1 month after the 1st time consultant):

Date: ……../……./…….. With supporter for treatment participate: Yes ☐ No ☐

Adherence level to treatment after the 1st counseling: Good (>95%) ☐ Not good (<95%) ☐

If the patient does not comply well, state the reason and solution:

Reason for adhering to treatment is not good	Solutions

The 3rd consultation to improve adherence (1 month after the 2nd time consultant):

Date: ……../……./…….. With supporter for treatment participate: Yes ☐ No ☐

Adherence level to treatment after the 2nd counseling: Good (>95%) ☐ Not good (<95%) ☐

If the patient does not comply well, state the reason and solution:

Reason for adhering to treatment is not good	Solutions

Patient adherence level after 3 time counseling sessions: : Good (>95%) ☐ Not good (<95%) ☐

Is the VL test repeated? : Yes ☐ No ☐

Sampling date: ____ / ____ / ____ Results: ……. copies/ ml

If the patient does not adherence well: the most important factor causing the patient not to adherence well

(choose 1): Behavior ☐ Cognitive ☐ Emotional ☐ Socio-economic status ☐

Will continued counseling to improve adherence? Yes ☐ No ☐ (*If yes, use new sheet*)

Testing for HIV drug resistance: Yes ☐ No ☐

Date of testing: ……../……../……

Result: ☐ No resistance to current regimen

☐ Resistance to current regimen (details: ……)

Clinical decision:

Keep the same treatment regiment

Switch to second-line regimen Start date: ___ / ___ / ___

Second-line (or 3) drug regimen: _____

Consulting staff

Date…. / …… / …… ..

(sign, clearly state full name)

Appendix 3. HIV drug resistance test report

Patient's information

Name: Sex:

Date of birth: Hospital patient ID:

Viral load test latest date: Viral load test result: _____copies/mL

ART regimen:_____

Drug resistance test

Sample collection date: Type of sample:

Drug resistance test date: Sample (ID):

Sequencer platform: Sequencing method: ☐Sanger ☐NGS

Result:

NRTI mutation	V75VM, M184V, T215TFIS	**PI mutation**	
NRTI resistance	ABC -Low-Level Resistance AZT- High-Level Resistance FTC- High-Level Resistance 3TC- High-Level Resistance TDF- Susceptible	**PI resistance**	ATV/r DRV/r LPV/r
NNRTI mutation		**INSTI mutation**	
NNRTI resistance	EFV NVP	**INSTI resistance**	BIC CAB DTG RAL

HIV drug resistance algorithm: Stanford University HIV Drug Resistance Database (Version:)

Note/Recommendation:……

……..

……..

……..

Date……

Name of laboratory technician Name of Head of laboratory

Signature

Table of mutation scoring (Optional)

Drug resistance mutation scores of NRTI

Rule	ABC	AZT	FTC	3TC	TDF
Total					

Drug resistance mutation scores of NNRTI

Rule	NVP	EFV
Total		

Drug resistance mutation scores of PI

Rule	ATV/r	DRV/r	LPV/r
Total			

Drug resistance mutation scores of INSTI

Rule	BIC	CAB	DTG	RAL
Total				