Practice Guideline

Thai national guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents 2010

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In Thailand, more than 150,000 patients are currently treated with antiretroviral drugs under the support of the National AIDS Program (NAP). The appointed Adults and Adolescents Committee consisted of 28 members who are experts in HIV research, patient care or health care policy. Relevant published literature, guidelines, and the most recent relevant clinical trials presented internationally were reviewed. Several peer review and clinical studies conducted in Thailand were included in the review process. Special considerations for patients with co-infection of tuberculosis or hepatitis B were incorporated. Appropriate cut-off of CD4+ T-cell counts when to commence ART among Thai patients have been considered. It is now recommended to start ART at CD4+ T-cell count <350 cells/mm³. For treatment-naïve patients, the preferred initial therapy is a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen containing lamivudine plus zidovudine or tenofovir. Stavudine will be phased out in a two-year plan at the national program level. Viral load and CD4+ T-cell counts should be monitored at least once and twice a year. To achieve long-term treatment success, enhancing adherence together with the proper management of antiretroviral-related toxicity is critical. In summary, the major changes from the Thai 2008 guidelines include commencing ART earlier. ART is recommended regardless of CD4+ T cell count if patients have an indication to treat their HBV co-infection. Preferred first regimen uses AZT or TDF, not d4T as the NRTI-backbone. Furthermore, efavirenz is now considered a preferred NNRTI, along with nevirapine.

Keywords: Adolescent, adult, antiretroviral, HIV, Thai guidelines

HIV-1 antiretroviral therapy (ART) has evolved and improved significantly since the advent of combined ART. Optimal management of ART has resulted in substantial reductions in morbidity, mortality, and health care utilization [1, 2]. Benefits from ART have been proven in resource-limited settings including Thailand [3-6] where generic antiretroviral drugs are

available at a much lower cost [7, 8]. However, there is no ideal ART regimen. Different regimens may have efficacy profiles, adverse effects, and/or drug-drug interactions, thus it can be difficult for non-specialized physicians to manage patients on ART. These problems continue to limit the effectiveness of ART in resource-limited settings [9]. Currently, more than 150,000 patients are treated with ART under the National AIDS Program (NAP) in Thailand. The Thai AIDS Society (TAS) previously launched recommendations in 2008 for the use of ART in HIV-1 infected adults and adolescents [10]. Significant

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changes including recommended antiretroviral regimens and optimal time of initiation have been addressed based on recent literature, as reflected in the new international guidelines [11, 12].

A number of recommendations of those updated international guidelines are not implementable in developing countries such as Thailand. The Ministry of Public Health (MOPH), the National Social Health Office (NHSO), and the Thai AIDS Society (TAS) therefore appointed The Thai National HIV Guidelines Working Group (TNHIVWG) to update Thai Guidelines based on their expertise in HIV clinical research, patient care, patient insight, and government policy in Thailand. The Adults and Adolescents Committee consists of 28 members. Relevant published literature and guidelines as well the most recent relevant clinical trials presented internationally were reviewed. Several peer reviewed published clinical studies conducted in Thailand were included in the reviewing process. The recommendations were based on the strength of evidence and the availability of antiretroviral agents through the NAP. Published studies, that are relevant and applicable to Thailand in particular, have been taken into consideration. The new guidelines were drafted by the committee and reviewed by the (TNHIVWG). These Guidelines focuses on practical key recommendations, i.e. when to initiate ART in adults and adolescents with HIV-1 infection; which regimens are preferred initial treatment; how to monitor the treatment response; what are common adverse effects; how to diagnose treatment failure; what are the concepts of selecting ART in patients with treatment failure; and selected special considerations in specific patients.

Antiretroviral therapy for treatment-naïve HIV-1 infected adults and adolescents

Patient evaluation and preparation prior to initiating antiretroviral therapy

Histories of current and prior antiretroviral agents (ARVs) including zidovudine (AZT) and single dose nevirapine (NVP), particularly during pregnancy, should be reviewed. Selection of the optimal regimen for HIV-1 infected individuals is based on assessment of efficacy, accessibility, related adverse effects, underlying diseases (e.g. diabetes, hypertension), co-infections (TB, HBV), and the potential for drug-drug interactions. Proper patient counseling is essential for life-long therapy and long-term and durability of the treatment success. This includes adherence, the potential risk of adverse drug effects or immune

reconstitution inflammatory syndrome (IRIS) following ART; particularly in patients with advanced clinical stage or CD4+ T-cell <100 cells/mm³ [13, 14] and long-term ARV-related complications. Baseline evaluation should include complete blood count, CD4+ T-cell count, plasma HIV-1 RNA (if available), fasting blood glucose, serum lipid profile (total cholesterol, LDL, HDL), AST, ALT, serum creatinine, HBsAg, VDRL, urinalysis, chest X-ray, and PAP smear (in women). Anti-HCV antibody should be tested in patients with a history of intravenous drug use [15, 16]. In patients with CD4+ T-cell count <50 cells/mm³, a fundoscopic examination to identify cytomegalovirus (CMV) retinitis is recommended.

Initiation of antiretroviral therapy

The ultimate goal of ART is to achieve maximal and durable plasma HIV-1 viral load (VL) suppression to an undetectable level of <50 copies/mL. Long-term durability of viral suppression has been documented in various settings of resource levels including Thailand [5, 17-22]. A cohort of up to 4000 patients from Denmark has shown that for a young person diagnosed with HIV infection in the late ART era, the estimated median survival is more than 35 years [23]. This information is important to motivate our patients for their long-term commitment in treatment adherence.

When to start antiretroviral therapy

A recommendation of when to start ART is fundamentally based on patient's symptoms [24, 25] and CD4+ T-cell counts, as shown in **Table 1**. The appropriate cut-off of CD4+ T cell count for when to start ART among Thai patients has been reconsidered. Recent cohort studies provide evidence supporting the benefit of ART in reducing AIDS- and non-AIDS associated morbidity and mortality in patients with CD4+ T cell counts of less than 350 cells/mm³ [26-29]. Moreover, the only recent randomized trial that was conducted in Haiti known as "CIPRA HT 001" provides strong support to initiate ART before the CD4 count falls below 350 cells/mm³ [30]. The earlier ART is initiated, the sooner the patients will achieve adequate immune status to prevent morbidity and mortality from opportunistic infections. This has also been demonstrated in a Thai setting [31]. In addition, accessibility to ART has been supported in Thailand. Thus, it is recommended that adults or adolescents with HIV-related symptoms or AIDS or with a CD4+ T-cell count <350 cells/mm³ should initiate treatment with ART.

Table 1. Indications for initiation of antiretroviral therapy (ART).

Clinical Presentation	CD4+ T-cell counts (cells/mm ³)	Recommendations
AIDS-defining illness*	Any value	Treat
HIV-related Symptomatic**	Any value	Treat
Asymptomatic	<350	Treat
Asymptomatic	≥350	Defer treatment; follow up clinical status and monitor CD4+ T-cell count every 6 months
Pregnancy	Any value	Treat, Discontinue ART after delivery if pre-treatment CD4+ T-cell count is ≥350 cells/mm ³

*as described in the 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults [24] and with penicilliosis, which is considered as AIDS-defining illness in Thailand [25]. **oral candidiasis, pruritic papular eruptions (PPE), unexplained fever or diarrhea > two weeks, >10% unexplained weight loss in 3 months, or herpes zoster involved > two dermatomes.

Special considerations

Pregnant women with HIV infection

ART is recommended for pregnant women with HIV-1 infection at any CD4+ T cell count. ART should be discontinued after delivery for those in whom the pre-treatment CD4+ T-cell count was ≥350 cells/mm³.

Other special settings with CD4+ T cell counts >350 cells/mm³

The panel recommends considering initiating ART in the following special settings regardless of a patient's CD4+ T cell count level: HBV or HCV co-infection when treatment for HBV or HCV and in patients older than 50 years with co-morbid diseases. To avoid over-prescribing of ARVs, expert consultation is recommended for those who are discordant couples, and in those with HIV-associated nephropathy.

Preferred initial antiretroviral regimen (Table 2)

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens are recommended as preferred first-line treatment. The efficacy of generic fixed-dose combination (FDC) NVP-based regimens has been well demonstrated [7-9, 32]. Together with its affordable cost and simplicity, it is recommended as preferred first regimen. An efavirenz (EFV)-based regimen that can be given once-daily is also recommended as another preferred first regimen. EFV is not recommended for use in the first trimester of pregnancy or in sexually active women with

childbearing potential who are not using effective contraception. In patients who cannot tolerate NVP and/or EFV, ritonavir-boosted lopinavir (LPV/r) is a recommended alternative. To achieve good adherence, patients should be advised to take the correct dosage of ARVs, to avoid missing any doses and to take the medications at the same time every day (i.e., every 12 hours for twice-daily regimens or every 24 hours for a once-daily regimen). Indinavir is no longer recommended due to its high rate of renal stones and toxicities.

For NRTI, zidovudine (AZT) or tenofovir (TDF) in combination with lamivudine (3TC) is recommended as the preferred backbone. Stavudine (d4T) is no longer recommended as first-line drug due to its high rate of toxicities. The Thai NAP has positioned a two-year phase out policy for patients who have been taking d4T [33, 34]. Patients who have d4T-related lipoatrophy should switch to TDF, while their VL is undetectable. Those who have no d4T toxicity may switch to AZT.

In HIV-1/HBV co-infected patients, tenofovir (TDF) + 3TC or emtricitabine (FTC) is recommended. Abacavir (ABC) + 3TC and didanosine (ddI) + 3TC are considered as alternatives NRTI-backbones for patients who cannot tolerate the preferred NRTI combinations. TDF is recommended in patients who cannot tolerate AZT, or have progression of lipodystrophy. Currently available ARVs in Thailand and the recommended dosages are summarized in **Table 3**.

Table 2. Recommended preferred and alternative first ART regimens.

NRTIs		NRTIs	PIs
Preferred			Preferred
AZT + 3TC		EFV ⁽⁴⁾	LPV/r
TDF + 3TC/FTC ⁽¹⁾		NVP ⁽⁵⁾	
Alternative		or (if patient cannot tolerate NNRTIs)	Alternative
ABC + 3TC ⁽²⁾			ATV/r
d4T + 3TC ⁽³⁾			DRV/r
ddI + 3TC			SQV/r

All ARVs in the above table are listed in alphabetical order. ⁽¹⁾TDF should be used in caution in patients with abnormal creatinine clearance and in elderly patients. TDF + 3TC/FTC is recommended in patients with HBV co-infection [2]. ⁽²⁾ABC can cause hypersensitivity reactions and should not be used with NVP. ⁽³⁾d4T, if used, should be replaced with another NRTI after 6-12 months. ⁽⁴⁾It cannot be used in the first trimester of pregnancy. ⁽⁵⁾NVP should be used with caution in females with CD4+ T cell counts >250 cells/mm³.

Table 3. Currently available ARVs in Thailand and recommended dosages.

Classes	Drugs	Preparations	Dosages
Nucleoside reverse transcriptase inhibitors (NRTIs)	abacavir (ABC)	300 mg	300 mg every 12 hours, or 600 mg every 24 hours
	didanosine (ddI)	chewable buffered tablets (125, 200 mg), enteric coated capsule (250, 400 mg)	250 mg 1 hour before meal every 24 hours for weight <60 Kg., or 400 mg 1 hour before meal every 24 hours for weight ≥60 Kg.
	lamivudine (3TC)	150, 300 mg	300 mg every 24 hours, or 150 mg every 12 hours
	stavudine (d4T)	30 mg	30 mg every 12 hours
	tenofovir (TDF)	300 mg	300 mg every 24 hours
	TDF/emtricitabine (FTC)	300/200 mg	one tablet every 24 hours
	zidovudine (AZT)	100, 250, 300 mg	200-300 mg every 12 hours
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	efavirenz (EFV)	200, 600 mg	600 mg every 24 hours before bedtime
	etravirine (ETR)	100 mg	200 mg every 12 hours
	nevirapine (NVP)	200 mg	200 mg every 12 hours
Protease inhibitors (PIs)	atazanavir (ATV)	300 mg	300 mg + RTV 100 mg every 24 hours with food*
	darunavir (DRV)	300 mg, 400 mg	600 mg + RTV 100 mg every 12 hours with food, or 800 mg + RTV 100 mg every 24 hours with food**
	lopinavir/ritonavir (LPV/r)	100/25, 200/50 mg	400/100 mg every 12 hours with food, or 800/200 mg every 24 hours with food**
	ritonavir (RTV)	100 mg	Only used as PI booster in the regimen
	saquinavir (SQV)	500 mg	1000 mg + RTV 100 mg every 12 hours with food, or 1500 mg + RTV 100 mg every 24 hours with food**
Integrase inhibitors	raltegravir (RAL)	400 mg	400 mg every 12 hours

*when used with TDF or EFV, use with RTV only; avoid taking with antacids, H2-blocker or proton pump inhibitors.

**once daily dosing is recommended for ARV-naïve patients only.

Treatment-naïve HIV-1 patients with opportunistic infections (OIs)

Although these new guidelines recommend starting treatment earlier, in reality, a significant number of patients are clinically advanced when first seeking medical care. Starting ART in patients with advanced HIV disease, low CD4+ T-cell count with or without active opportunistic infections (OIs) puts patients at risk for drug-related toxicity, or immune reconstitution inflammatory syndrome (paradoxical IRIS). Appropriate timing to initiate ART in patients with active OIs is not yet well established. In the setting of cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy (PML), and Kaposi sarcoma, the benefits of early ART outweigh any increased risk, and a recommended ART regimen should be started as soon as possible. In cases of *Mycobacterium avium* complex (MAC), PCP, cryptococcal meningitis, and CMV retinitis, we recommend to defer ART initiation following the OI therapy by approximately two to four weeks. In patients who have an OI occurring within or after 12 weeks of starting ART (unmasking IRIS), treatment for the OI should be started while continuing ART.

Antiretroviral therapy in treatment-naïve HIV-1 / TB co-infection

Tuberculosis (TB) is the most common reactivated infectious disease in HIV-1 infected patients. A rifampicin-based anti-TB regimen is essential. Nonetheless, rifampicin induces hepatic cytochrome P-450 resulting in a significant decrease of plasma NNRTI and protease inhibitor (PI) levels [35, 36]. In addition, ARVs and anti-TB medications have overlapping toxicities, particularly cutaneous and hepatic adverse events. Drug-drug interactions and additive toxicity complicate treatment of this co-infection. The importance of treatment adherence to both ART and anti-TB regimens for a successful treatment outcome must be convincingly emphasized

to patients. Liver and kidney function should be tested prior to the initiation of ART.

A recent study has demonstrated that initiation of ART during tuberculosis therapy significantly improved survival compared to when ART was initiated after the completion of TB treatment [37]. However, the optimal timing for initiating ART during TB treatment remains unknown. Simultaneous initiation of both ART and therapy for TB should be avoided due to the increased risks of IRIS and additive toxicity. The panel recommends deferring ART until anti-TB treatment has been started for at least four to eight weeks [38-40].

Indications for when to initiate ART in HIV-1/TB co-infection are summarized in **Table 4**. Patients who are treated with non-rifampicin containing anti-TB regimens, the ART guidelines are applicable same as for non-TB patients. For patients who are treated with rifampicin-containing anti-TB regimen, EFV-based ART is recommended. The dosage of EFV is 600 mg/day for weight <60 kg and 800 mg/day for weight ≥60 kg [32]. A number of studies in Thailand have shown that NVP at a normal dose of 400 mg/day can be used effectively with rifampicin [36, 40, 41]. One study found that an increase of NVP dose to 600 mg per day, with a lead-in of 200 mg twice daily, was associated with a high rate of hepatotoxicity and is therefore not recommended. Thus, a standard dose of NVP is an alternative to EFV for patients treated with rifampicin, and lead-in NVP treatment (200 mg/day) for the first 14 days may be not necessary [36, 42]. If the patient cannot tolerate EFV- or NVP-containing ART and cannot wait until the completion of TB treatment (e.g. CD4+ T-cell count <100 cells/mm³), one should consider using a non-rifampicin containing anti-TB regimen PI-containing ART. It may not be necessary to switch NVP to EFV in patients who have been on NVP and must be treated with rifampicin, but they need monitoring.

Table 4. Indications for initiation of ART in patients with HIV and tuberculosis (TB) co-infection.

CD4+ T cell counts (cells/mm ³)	Recommendations
<200	Start ART 2-8 weeks after the initiation of TB treatment
200 - <350	Start ART 2 months after the initiation of TB treatment
≥350	Defer ART Follow up clinical status and monitor CD4+ T-cell count every 6 months

Monitoring antiretroviral therapy

Clinical review and relevant laboratory and adherence monitoring are crucial to detect early treatment failure or drug-related adverse effects. **Table 5** summarizes the recommended laboratory monitoring. The best laboratory tools to evaluate treatment response are plasma HIV-1 VL and CD4+ T-cell count. VL is more accurate and reliable than CD4+ T-cell count to monitor treatment response and for early detect treatment failure [12, 43]. Effective ART regimens and high level of adherence result in suppression of VL to <50 copies/mL by six months of ART [44]. A detectable VL after six months of ART or a rebound in VL after achieving an undetectable level should prompt evaluation of the patient's adherence and any other causes of treatment failure. In treatment failure, a rebound of VL precedes the decline of CD4+ T-cell counts by several months.

It is recommended to monitor VL regularly for at least every six months in the first year of ART and at least yearly later on. Patients with poor adherence should be advised to take the medications well, and

then have a reassessment of plasma VL in a few weeks to identify treatment failure. CD4+ T-cell count monitoring is important to evaluate immune restoration after ART and to determine when to stop OI prophylaxes. CD4+ T cell count should be performed every six months.

In general, CD4+ T cell counts usually increase by approximately 50-150 cells/mm³ per year of ART [45], until reaching the normal levels. However, some patients may experience a slower increase of CD4+ T cell counts particularly when ART were initiated at very low CD4 count levels. Recent studies have demonstrated that CD4+ T cell criteria, either at 25% or 50% declining from baseline levels, are not accurate for determining treatment failure [46-48]. More importantly, when using CD4+ T cell criteria alone, misclassification of treatment failure among patients with a CD4 count that has declined, but with undetectable plasma VL are common [48]. For this reason, monitoring CD4+ T cell count alone is not recommended.

Table 5. Recommended laboratory monitoring after initiation of ART.

Laboratory tests	Recommended time for the test		Note
	First year of ART	Following years	
CBC, CD4+ T-cell count	at 6 and 12 months	every 6 months	
Plasma VL	<i>First regimen:</i> at 6 and 12 months <i>The next regimens:</i> at 3 and 6 months	every 12 months (every 6 months is preferred) every 12 months	should be performed before switching of ARVs due to adverse effects
FBS	at 6 and 12 months	every 6 months	
ALT	at 6 and 12 months	every 6 months	should be performed at 3 months if NNRTI is used
Creatinine*	at 6 and 12 months	every 6 months	strongly recommended if TDF is used
Lipid profile (TC, TG, LDL, HDL)	at 6 and 12 months	every 6 months	
Urinalysis	-	-	should be performed every 12 months if TDF is used
CXR	-	-	perform when clinical status indicates
Pap smear	at 12 months	every 12 months	perform when clinical status indicates

*for calculation of creatinine clearance.

Adverse effects of ARVs and their management

Treatment of HIV-1 infection with ART represents a complicated balance between the benefits of maximal durable viral suppression and the risks of adverse drug effects. ARV-related adverse effects occur across a broad spectrum. The most common reason for switching or discontinuing ART is adverse effect [49]. Adverse effects may occur early or late following ART initiation. Some of these effects can affect a patient's quality of life and the medication adherence. Common adverse effects from ARVs are summarized in **Table 6**. ARV that causes adverse effects should be replaced with other ARV in the same class but does not have overlapping adverse effects. To minimize the risk of subsequent HIV drug resistance to NNRTIs, the NRTI backbone should be continued for seven to 10 days if NNRTI in the same regimen is discontinued due to adverse effect [50]. In case of severe adverse effects, e.g. lactic acidosis, or Stevens-Johnson syndrome, all ARVs should be stopped immediately. Lipodystrophy is one of the most common

long-term adverse effect of d4T, some boosted PIs and EFV in particular [33, 34, 51]. Early switching of the causative ARV may avoid irreversible lipodystrophy. Dyslipidemia is common among patients taking PIs, EFV, and d4T [52-54]. Monitoring and management of this metabolic complication, as well as other conventional risks, can minimize the risk of cardiovascular diseases.

Immune reconstitution inflammatory syndrome (IRIS)

IRIS is a syndrome that usually occurs in patients with immune restoration after the initiation of ART at low CD4+ T cell counts. IRIS can be categorized into two major clinical patterns: 1) Paradoxical IRIS occurs in a clinical setting when a completely or partially treated OI recurs or worsens following ART initiation; and 2) Unmasking IRIS is defined as a clinical activation of an unrecognized and previously untreated OI. It should be noted that IRIS could also occur as a non-infectious inflammatory disease. In Thailand,

Table 6. Adverse effects of ARVs.

Classes	Drugs	Adverse effects
Nucleoside reverse transcriptase inhibitors (NRTIs)	abacavir (ABC)	hypersensitivity reactions
	didanosine (ddI)	peripheral neuropathy, pancreatitis, nausea, vomiting, hepatitis, hyperlactatemia, lactic acidosis
	lamivudine (3TC)	nausea, vomiting (very rare)
	stavudine (d4T)	peripheral neuropathy, lipoatrophy, dyslipidemia, hyperlactatemia and lactic acidosis
	tenofovir (TDF)	renal toxicity, Fanconi syndrome, nephrogenic diabetic insipidus
	emtricitabine (FTC)	nausea, vomiting, diarrhea, abdominal distension, weakness
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	zidovudine (AZT)	nausea, vomiting, headache, insomnia, asthenia, bone marrow suppression (macrocytic anemia, neutropenia), nail hyperpigmentation
	efavirenz (EFV)	rash, central nervous system symptoms (dizziness, somnolence, insomnia, abnormal dreams, confusion), dyslipidemia, increased transaminases, teratogenicity
	etravirine (ETR)	rash, nausea, vomiting, abdominal pain
	nevirapine (NVP)	rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatotoxicity
Protease inhibitors (PIs)	atazanavir (ATV)	indirect hyperbilirubinemia, prolonged PR interval, first degree AV block (uncommon)
	darunavir (DRV)	nausea, vomiting, dyslipidemia,
	lopinavir/ritonavir (LPV/r)	nausea, vomiting, diarrhea, dyslipidemia especially hypertriglyceridemia, lipodystrophy
	ritonavir (RTV)	nausea, vomiting, diarrhea, dyslipidemia especially hypertriglyceridemia, lipodystrophy
	saquinavir (SQV)	nausea, vomiting, diarrhea, headache, dyslipidemia, increased transaminases, lipodystrophy
Integrase inhibitors	raltegravir (RAL)	diarrhea, headache, nausea

the majority of IRIS is caused by *Mycobacterium tuberculosis*, MAC, and *Cryptococcus neoformans* [13, 14, 55-57]. The clinical manifestations of IRIS usually appear within the first three months following ART initiation. Patients with baseline CD4+ T-cell counts and fewer than 50 cells/mm³ have a high risk of IRIS [58]. Due to the non-specific clinical manifestations, physicians must be vigilant to diagnose IRIS. However, as part of the differential diagnosis, other causes such as adverse effects of ART or treatment failure with deterioration of HIV status must be excluded. Most patients with IRIS recover within two to four weeks and do not need to interrupt ART. Treatment of OI should be administered as indicated. Non-steroid anti-inflammatory drugs or systemic corticosteroids may be given according to the severity of inflammation [59].

Antiretroviral treatment failure

Diagnosis of treatment failure

Treatment failure is generally associated with virological failure, immunologic failure, and/or clinical progression. Nonetheless, virological failure is the most sensitive measure of early treatment failure. Early diagnosis can prevent the accumulation of drug-resistant associated mutations (RAMs) and preserve antiretroviral options. Therefore, the panel therefore primarily recommends using virological failure to define treatment failure. The Thai national program provides free plasma VL tests two times in the first year, then once a year. Furthermore, it recommends monitoring patients who are taking ART. The criteria for treatment failure are plasma VL >400 copies/mL after six months of ART with good adherence, or plasma VL >50 copies/mL after 12 months of ART with good adherence, or a rebound of plasma VL to >50 copies/mL occurring at any time after achieving VL <50 copies/mL. Patients who have a plasma VL of 51-1000 copies/mL may be in a very early stage of treatment failure or may be experiencing a transient viremia (viral blip, which is not associated with treatment failure). These patients should be counseled on the importance of adherence to ART and their plasma VL should be reassessed within two to three months. Although treatment failure is suggested when plasma VL is >50 copies/mL, HIV-1 drug resistance genotype tests can only be successfully analyzed when plasma VL is >1000 copies/mL. Based on cost-effectiveness considerations, the panel recommends HIV-1 drug resistance genotype testing when the

plasma VL >2000 copies/mL. It is important that the drug resistance genotype test should be performed while patients are still taking the ART. Discontinuation of ART prior to the test will result in a decrease or loss of sensitivity to detect the resistant viruses due to repopulation of wild-type virus.

Immunological failure had previously been used as criteria for treatment failure and is still used in various resource-limited settings. Recent studies however, have clearly demonstrated that defined criteria of CD4+ T cell decline have a low sensitivity and specificity to detect treatment failure [46-48, 60]. More importantly, patients usually accumulate resistance mutations when immunological failure occurs. In addition, some patients have a decrease or delayed increase of CD4+ T-cell count despite undetectable VL that may lead to a misdiagnosis of treatment failure and result in unnecessary ART switching. *Clinical failure* is the most delayed endpoint to diagnose treatment failure and should not be used in place of VL and CD4+ T-cell count. Patients usually have virological and immunological failure for months or even years before the clinical failure occurs. IRIS needs to be excluded before a diagnosis of clinical failure. Once again, it is clear that early detection of treatment failure, particularly using monitoring of plasma VL, can preserve the future options for ART [61].

Antiretroviral therapy for patients with treatment failure

Recent studies have demonstrated that a high proportion of treatment-experienced patients can achieve a VL level of <50 copies/mL when at least two active antiretroviral agents are added [43, 62]. There currently are more new classes and more potent ARVs in the former classes available. Therefore, the ultimate aim to treat treatment-experienced patients is to re-achieve VL suppression to <50 copies/mL [43]. When this goal is not achievable, stability of CD4+ T-cell count and clinical status may be maintained for a period of time with a selection of a suitable ART regimen, based-on resistance test guidance and probably with a recycling of 3TC to minimize HIV-1 viral fitness.

A careful review of the previous ARV history, all previous HIV-1 genotype resistance test results, potential drug-drug interactions, relevant comorbidities, ARV availability, and a patient's adherence is very crucial to properly plan for the next ART

regimen. For selecting subsequent therapy in patients with treatment failure, ideally, a new regimen should include three active ARVs. If this is not possible, at least two active drugs are required. To prevent rapid development of HIV drug resistance, using or adding only one active drug in the new regimen is not recommended. After commencing the new regimen, treatment adherence, drug interaction, and tolerability should be assessed and plasma VL should be tested at least three months later.

Almost all Thai patients started treatment with NNRTI-based ART, thus failing an NNRTI-based regimen is much more common than failing a PI-based regimen. In patients who failed an initial NNRTI-based regimen with 3TC included, NNRTI resistance mutations and M184V/I (3TC resistance) are commonly observed. Thymidine analog-associated mutations (TAMs) including M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E, can be found in more than one-third of patients. K65R and Q151M are observed in patients with late detection of virological failure when plasma VL was more than 4 Log₁₀ (Copies/mL) [59, 63, 64]. There is no controlled study to address appropriate second-line treatment options in patients failing NNRTI-based regimens. Therefore, the following recommendation is solely based on expert opinion. In a setting like Thailand where new ARV classes such as integrase inhibitors and CCR-5 receptor inhibitors are not affordable, a boosted-PI in combination with two active NRTIs guided by the results of resistance genotype test [65] should be used as the second ART regimen. In patients who have only one active NRTI available, 3TC may be considered for inclusion in the second regimen together with boosted lopinavir plus the active NRTI. For late failure patients who have no active NRTI available at all, it is not known whether a mono-boosted PI will result in durable viral suppression like with a boosted PI in combination with two recycled NRTIs. Recent clinical trials showed no benefit of double-boosted PIs over single-boosted PIs [36, 60,

66-69]. Expert consultation or referral to a second-line randomized trial is therefore advised. In patients failing an initial PI-based regimen, NRTI resistance mutations are commonly observed. PI resistance-associated mutations are rare in boosted-PI regimens. However, PI resistance-associated mutations are accumulated in patients with late detection of virological failure. Choosing a new PI in the new regimen is based on the number and patterns of PI resistance mutations [70]. An active PI, boosted with ritonavir, should be used as a second regimen combined with the two other active drugs, either NRTI or NNRTI, as indicated by the genotype resistance test results. **Table 7** summarizes the options for the second-line ART regimens.

In patients with multiple drug class treatment failures, multiple drug resistance to NRTIs, NNRTIs and PIs are common. The ideal next regimen is to use at least two new active ARVs, such as darunavir (second generation PI), etravirine (second generation NNRTI), and/or raltegravir [71]. Strategies to increase access to new ARVs in Thailand in the near future are being considered in the National AIDS Program. In cases where there is no active drug option available, expert consultation or referral to an appropriate clinical trial is advised. While waiting for new drugs, a holding regimen consisting of 3TC and other NRTIs may be considered.

Conclusion

The panel has recommended a number of major changes from the Thai 2008 guidelines. Those changes include commencement of ART earlier at CD4+ T cell count <350 cells/mm³, ART initiation is recommended regardless of CD4+ T cell count if patients have an indication to treat their HBV co-infection, preferred first regimen uses 3TC with AZT or TDF, not d4T as the NRTI-backbone, and efavirenz is now considered a preferred NNRTI, along with nevirapine.

Table 7. Recommended second-line ART regimens for patients with treatment failure.

First regimens	Recommended second regimens
2 NRTIs + NNRTI	Boosted PI + 2 active NRTIs indicated by genotype testing
2 NRTIs + boosted PI	1) active boosted PI + 2 active NRTIs indicated by genotype testing 2) active boosted PI + 1 NNRTI ± 1 NRTI indicated by genotype testing 3) NNRTI + 2 active NRTIs indicated by genotype testing This option can be used only when there are 2 active NRTIs and the patient has never been exposed to NNRTI, or NRTI monotherapy or duotherapy.

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