Special Article

Guidelines for Antiretroviral Therapy in HIV-1 Infected Adults and Adolescents: The Recommendations of the Thai AIDS Society (TAS) 2008

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Background: *More than 100,000 patients have been treated, since the implementation of the National Universal Coverage for antiretroviral therapy (ART) in Thailand. Although there are several comprehensive guidelines available internationally, there is a need to have guidelines that can be implemented in Thailand.*
Material and Method: *The guidelines were developed by a panel of 17 members who are the experts on HIV research and/or HIV patient care and appointed without incentive by the Thai AIDS Society (TAS). The recommendations were based on evidences from the published studies and availability of antiretroviral agents. Published studies that are relevant and applicable to Thailand in particular have been taken into consideration.*
Results: *The recommendations include: when to start ART; what to start; how to monitor the therapy; adverse effects and its management; diagnosis of treatment failure; and antiretroviral treatment options in patients with treatment failure. ART in special circumstances, i.e. patients with co-infection of tuberculosis or hepatitis B virus, is also included. Appropriate level of $CD4^+$ T-cell count to start ART among Thai patients has been considered carefully. The authors recommend to start ART at $CD4^+$ T-cell count < 200 cells/mm^3.*
Conclusion: *ART should be initiated in adults and adolescents HIV-1 infected patients with a history of HIV-related illness or AIDS or with a $CD4^+$ T-cell count < 200 cells/mm^3. For treatment-naive patients, the preferred initial therapy is a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen. $CD4^+$ T-cell count and viral load should be monitored for at least twice and once a year, respectively. Proper management of antiretroviral-related toxicity and enhancement of adherence are crucial for the long-term success of ART.*

Keywords: *HIV, Antiretroviral therapy, Guidelines, Thailand, TAS, 2008*

J Med Assoc Thai 2008; 91 (12): 1925-36
Full text. e-Journal: *http://www.medassocthai.org/journal*

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Combination antiretroviral therapy (ART) has evolved the management of HIV-1 infection, which has resulted in substantial reductions in morbidity, mortality, and health care utilization[1,2]. This benefit from ART has been proved in resource-limited settings including Thailand[3-6], where generic drugs are widely used in initial ART regimens[7-9]. Highly active ART leads to sustained suppression of HIV-1 RNA replication, resulting in gradual increases in $CD4^+$ T-cell count. However, ART regimens are complex, have major adverse effects, can be difficult for clinicians to manage. These problems continue to limit the effectiveness of ART in resource-limited settings[10]. More than 100,000 patients have been treated, since the implementation of the National Universal Coverage for ART in Thailand. Although there are several comprehensive guidelines available internationally, there is a need to have guidelines that can be implemented in Thailand. The Thai AIDS Society (TAS) has made an effort to provide clinicians with current recommendations for the use of ART in HIV-1 infected adults and adolescents. A committee of Thai AIDS Society was appointed, based on expertise in HIV research and patient care in Thailand. Data published were identified and reviewed by members of the committee. New guidelines were drafted by a writing committee and reviewed by the committee.

The guidelines will focus on the practical keys of recommendations, i.e. when to initiate ART in patients with HIV-1 infection; which regimens are effective for the initial treatment of HIV-1 infection; how to monitor the treatment response; what are common adverse effects and how to manage; how to diagnose treatment failure; and what are the concepts of ART in patients with treatment failure. Some changes are updated from the 2007 Thai version according to the new data from publications and availability of antiretroviral agents (ARVs) in Thailand. ART in special circumstances, i.e., patients with co-infection of tuberculosis (TB) or hepatitis B virus (HBV), is also described.

ART in treatment-naive HIV-1 infected patients

Patient evaluation prior to initiation of ART

Histories of current and prior antiretroviral medications including zidovudine (AZT) and single dose nevirapine (NVP) exposure during pregnancy should be reviewed. Optimal regimen for HIV-1 infected individuals is based on availability of ARVs, affordability, cost of ARVs, adverse effects, other underlying diseases (e.g., HBV co-infection, TB), and potential drug-drug interactions. Patients should be counseled for the current prospects for life-long therapy, importance of adherence, and the possibility of adverse drug effects and immune reconstitution inflammatory syndrome (IRIS) following ART particularly in patients with an advanced clinical stage or $CD4^+$ T-cell < 100 cells/mm^3. Complete blood count, $CD4^+$ T-cell count, plasma HIV-1 RNA, fasting blood glucose, serum lipid profile, AST, ALT, serum creatinine, HBsAg, VDRL, urinalysis, chest X-ray, and PAP smear in women should be performed. Anti-HCV antibody should be tested in patients with a history of intravenous drug use[11]. Fundoscopic examination to evaluate for cytomegalovirus (CMV) retinitis for patients with $CD4^+$ T-cell count < 50 cells/mm^3 should be performed.

Initiation of ART

Decision to start ART is fundamentally based on the patient's symptoms and $CD4^+$ T-cell count, as shown in Table 1[12,13]. The appropriate cut-off of $CD4^+$ T cell count for when to start ART among Thai patients has been considered carefully. The decision has been made based on the fact that mean normal value of $CD4^+$ T-cell count is significantly lower among Thais compared to that of Caucasians[14,15]. A Thai cohort study although it has shown a minimal but significant benefit in the rate of reduction of AIDS progression or death when ART was commenced at $CD4^+$ T-cell count of 200-350cells/mm^3, however it is not as cost effective as the National Program. Whether to start ART at $CD4^+$ T-cell count of 200-250 cells/mm^3 for Thai patients is cost-effective requires further investigation. Thus, the authors recommend that adult or adolescent patients with HIV-related symptoms or AIDS or with a $CD4^+$ T-cell count < 200 cells/mm^3 should be initiated for ART.

Prophylaxis for opportunistic infections, e.g. *Pneumocystis* pneumonia (PCP), is indicated in patients who meet the indication for ART initiation but should not be commenced simultaneously with ART particularly in patients who will take nevirapine (NVP)-based regimen. Because both sulfamethoxazole/trimethoprim and NVP have a high rate of similar life-threatening adverse effects i.e., Stevens-Johnson syndrome in HIV-infected patients. It should be initiated at a duration of 2-4 weeks before or after ART initiation. The ultimate goal of ART is to maximally and durably suppress the HIV-1 viral load (VL) to undetectable level i.e. < 50 copies/mL. Long-term durability of viral suppression for more than 10 years has been documented[16]. Individuals who have been successfully

Table 1. Indications for initiation of ART

Clinical presentations	$CD4^+$ T-cell counts (cells/mm^3)	Recommendations
AIDS-defining illness*	Any value	Treat
Symptomatic**	Any value	Treat
Asymptomatic	< 200	Treat
Asymptomatic	200-350	Defer treatment; follow up clinical status and monitor $CD4^+$ T-cell count every 3 months
Asymptomatic	> 350	Defer treatment; follow up clinical status and monitor $CD4^+$ T-cell count every 6 months

* As described in 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults[12] and penicilliosis, which is considered as AIDS-defining illness in Thailand[13]
** Oral candidiasis, pruritic papular eruptions (PPE), unexplained fever or diarrhea > 2-4 weeks, or > 10% unexplained weight loss

virological suppressed with combined ART for more than 17 years has also been evidenced in a Thai setting. This information is essential in providing counseling to patients to motivate their long-term commitment in treatment adherence.

ARVs currently available in Thailand are summarized in Table 2[17]. Recommendations of ART regimens are shown in Table 3. Since efficacy of generic fixed-dose combination (FDC) of NVP-based regimen has been demonstrated[7-9,18], together with affordable costs and simplicity of the regimen, it is recommended as the preferred first regimen. NVP can be substituted with efavirenz (EFV), if the patient develops a severe rash or hepatotoxicity from NVP. EFV is not recommended for use in the first trimester of pregnancy or in sexually active women with child-bearing potential who are not using effective contraception. EFV can be substituted with indinavir (IDV)/ritonavir (RTV) or lopinavir/RTV (LPV/r), if the patient develops severe side effects from EFV. Patients should be advised that all dosage of any ARV regimen should never be missed and should be taken at the same time every day i.e., every 12 hours for twice daily regimen or every 24 hours for once-daily regimen.

Stavudine (d4T) has a better short term tolerability profile than AZT and more cost-effective than tenofovir (TDF); therefore it is recommended to include d4T in the initial backbone for the first 6 months of therapy. In Thailand, the authors recommend a FDC of d4T/lamivudine (3TC)/NVP for the first 6 months, and then switch to AZT/3TC/NVP FDC. Patients who can not tolerate d4T, AZT, or NVP shall be switched to AZT, TDF, or EFV, respectively. The nucleoside reverse transcriptase inhibitor (NRTI) backbone of TDF + 3TC or TDF + emtricitabine (FTC) are recommended for patients who cannot tolerate the preferred backbone or who have HIV-1/HBV co-infection. TDF should be preserved for treatment of HIV-1 resistant to other NRTIs except patients with HIV-1/HBV co-infection as above. 3TC + abacavir (ABC) backbone is recommended for patients who cannot tolerate other NRTI combinations or develop severe adverse effects from AZT, d4T, ddI and TDF. All NRTIs, except ABC, need dose-adjustment in patients with renal insufficiency[19]. Antiretroviral regimens not recommended are as follows: monotherapy or dual nucleoside therapy, d4T + AZT (antagonism *in vitro*), d4T + ddI (high incidence of toxicities: peripheral neuropathy, pancreatitis, and lactic acidosis), TDF + ddI (high failure rate), all triple-NRTI regimens (high failure rate), EFV in first trimester of pregnancy and women with significant childbearing potential, and Atazanavir (ATV) + IDV (additive or worsening hyperbilirubinemia).

ART in patients with opportunistic infections (OIs)

In the setting of cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy (PML), and Kaposi sarcoma, the benefits of early ART outweigh any increased risk, and potent ART should be started as soon as possible. However, in cases of TB, *Mycobacterium avium* complex (MAC), PCP, cryptococcal meningitis, and CMV retinitis, the authors recommend to wait for a response to OI therapy prior to initiating ART. The optimal time for initiating ART during treatment of TB remains unknown. Simultaneous initiation of both ART and therapy for TB should be avoided due to the increased risks of IRIS and additive toxicity. Most Thai HIV experts would wait at least 4-8 weeks before initiation of ART following OI therapy[20-22]. In patients who have an OI

Table 2. Currently available ARVs in Thailand and recommended dosage

Classes	Drugs	Preparations	Dosages
Nucleoside reverse transcriptase inhibitors (NRTIs)	zidovudine (AZT)	100, 250, 300 mg	200-300 mg every 12 hours
	lamivudine (3TC)	150, 300 mg	150 mg every 12 hours, or 300 mg once daily
	stavudine (d4T)	30 mg	30 mg every 12 hours
	didanosine (ddI)	chewable buffered tablets (125, 200 mg), enteric coated capsule (250, 400 mg)	250 mg once daily 1 hour before meal for weight < 60 Kg., or 400 mg once daily 1 hour before meal for weight ≥ 60 Kg.
	abacavir (ABC)	300 mg	300 mg every 12 hours, or 600 mg once daily
	tenofovir (TDF)	300 mg	300 mg once daily
	AZT/3TC	300/150 mg	every 12 hours
	3TC/ABC	300/600 mg	1 tablet once daily
	TDF/emtricitabine (FTC)	300/200 mg	1 tablet once daily
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	nevirapine (NVP)	200 mg	200 mg every 12 hours
	efavirenz (EFV)	200, 600 mg	600 mg once daily before bedtime
Fixed-dose combination of NNRTI + 2NRTIs	NVP/d4T/3TC*	200/30/150 mg	1 tablet every 12 hours
	NVP/AZT/3TC*	200/250/150 mg	1 tablet every 12 hours
Protease inhibitors (PIs)	indinavir (IDV)	200, 400 mg	400-800 mg + RTV 100 mg twice daily with food**
	ritonavir (RTV)	100 mg	use as PI booster in the regimen
	saquinavir (SQV)	500 mg	1000 mg + RTV 100 mg twice daily with food***, or 1500 mg + RTV 100 mg once daily with food [16]
	lopinavir/ritonavir (LPV/r)	soft gel capsule (sgc) 133.3/33.3 mg, tablet 200/50, 100/25 mg	3 sgc twice daily with food, or 2 (200/50) tab lets twice daily, or 4 (100/25) tablets twice daily with food
	atazanavir (ATV)	200, 300 mg	400 mg once daily with food, or 300 mg + RTV 100 mg once daily with food****
	darunavir (DRV)	300 mg	600 mg + RTV 100 mg twice daily with food
Fusion inhibitors	enfuvirtide (ENF)	90 mg (inj.)	90 mg inject subcutaneously twice daily
Integrase inhibitors	raltegravir (RAL)	400 mg	400 mg twice daily

* Combination of NNRTI and 2 NRTIs; ** At least 1500 mL/day of oral fluid is recommended for individual taking IDV to avoid the development of renal calculi and renal failure; *** Once daily dosing is recommended for ARV-naive patients only; **** When used with TDF or EFV, use with RTV only; avoid taking with antacids, H2-blocker or proton pump inhibitor

occurring within or after 12 weeks of starting ART, treatment for the OI should be started, and ART should be continued. When an OI occurs in the setting of virologic failure, OI therapy should be started, anti-retroviral resistance testing should be performed, and the ART regimen should be switched to the regimen which can achieve a better virologic control.

ART in patients with HIV/TB co-infection

Prior to initiation of ART

Rifampicin-based anti-TB regimen is essential for TB treatment in HIV-1 infected patients. Rifampicin induces hepatic cytochrome P-450 resulting in a decrease of plasma NNRTIs and PIs levels[23,24]. ARVs and anti-TB medications have overlapping toxicities, particularly cutaneous and hepatic toxicities. The authors should emphasize that adherence to both the ART and anti-TB regimens are essential for successful treatment.

Initiation of ART

Indications for initiation of ART in TB/HIV co-infection are summarized in Table 4. For a patient who has been treated with non-rifampicin containing anti-TB regimen, follows the above ART guideline in non-TB patients. For a patient who has been treated

Table 3. Recommended preferred and alternative regimens for initial ART

Type of regimens	2 NRTIs	NNRTI or PI
Preferred regimens	Fixed-dose combination of d4T/3TC/NVP (GPO-VIR S 30®)*	
	Fixed-dose combination of AZT/3TC/NVP (GPO-VIR Z 250®)	
	d4T* + 3TC	EFV
	AZT + 3TC	IDV/RTV**
		LPV/r**
Preferred regimens in HIV/HBV co-infection	TDF + 3TC or TDF/FTC	EFV
Alternative regimens	AZT + ddI	LPV/r
	ddI + 3TC	ATV ± RTV
	TDF + 3TC or TDF/FTC	SQV/RTV
	3TC + ABC	

* Suggest to switch d4T to AZT after using d4T for ≥ 6 months, to avoid long-term adverse effect, i.e. lipodystrophy, lactic acidosis, dyslipidemia; ** Used when patient cannot tolerate both NVP and EFV

Table 4. Indications for initiation of ART in patients with TB/HIV coinfection

$CD4^+$ (cells/mm^3)	Recommendations
< 100	Start ART as soon as the patient can tolerate anti-TB treatment
100-200	Start ART at 2 months after the initiation of TB treatment
200-350	Defer ART*, follow-up clinical status and monitor $CD4^+$ T-cell count every 3 months
> 350	Defer ART, follow-up clinical status and monitor $CD4^+$ T-cell count every 6 months

For patient with a $CD4^+$ T-cell count of 200- 250 cells/mm^3, some Thai HIV experts may commence ART at 2 months after the start of TB treatment especially if the patient cannot be tested for $CD4^+$ T-cell count at 3 months after initiation of TB treatment

with rifampicin-containing anti-TB regimen, EFV-based ART is recommended for treatment of HIV infection. The dosage of EFV is 600 mg/day for weight < 60 kg and 800 mg/day for weight ≥ 60 kg[23]. A number of studies in Thailand showed that NVP at a normal dose of 400 mg/day can be used effectively with rifampicin[22,24,25]. A 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, therefore is not recommended. Thus, a standard dose of NVP is an alternative to EFV for patient who has taken rifampicin and a lead-in NVP treatment (200 mg/d) for the first 14 days is not necessary[24,26]. If the patient cannot tolerate EFV- or NVP-containing ART and cannot wait until completion of TB treatment (e.g., $CD4^+$ T-cell count < 100 cells/mm^3), one should consider using non-rifampicin containing anti-TB treatment and PI-containing ART. Rifampicin-based anti-TB treatment can be used for a patient who develops TB and is already being treated with NVP-containing ART. It's not necessary to switch from NVP to EFV.

Monitoring of ART

After initiation of ART, it is necessary to monitor regularly to assess the treatment response and occurrence of adverse drug effects. Table 5 summarizes the recommended laboratory monitoring of ART. The best laboratory tools to evaluate treatment response are plasma VL and $CD4^+$ T-cell count. VL is more accurate and reliable than $CD4^+$ T-cell count to monitor treatment response. The aim of ART is to maintain the VL below the limits of detection (< 50 copies/mL)[19,27]. Effective regimens and high levels of adherence result in suppression of VL < 50 copies/mL by 4-6 months of ART[28]. Patients who achieve VL < 50 copies/mL had a better prognosis than patients who achieve VL < 400 but higher than 50 copies/mL. A detectable VL after 4-6 months of ART and a rebound in VL after achieving an undetectable level should prompt a careful evaluation of the patient's adherence to ART. In treatment failure, a rebound of VL precedes the decline of $CD4^+$ T-cell counts. Measures of VL should be obtained at regular intervals (e.g. every 6-12 months) to confirm that the VL level remains

Table 5. Recommended laboratory monitoring of ART

Laboratory tests	Recommended time for the test	
	First year of ART	Following years
CBC, $CD4^+$ T-cell count	at 6 and 12 months of ART	every 6 months
HIV-1 VL	at 6 and 12 months of ART	every 6-12 months
FBS	at 6 and 12 months of ART	every 6-12 months
AST, ALT	at 1*, 3, 6 and 12 months of ART	every 6-12 months
Cr.	at 3**, 6**, 9**, 12 months of ART	every 6*-12 months
Electrolytes**	at 12 months of ART	every 12 months
Lipid profile (TC, TG, LDL)	at 6 and 12 months of ART	every 6-12 months
Urinalysis	at 3**, 6** and 12 months of ART	every 12 months

* If patient takes NVP; ** If patient takes TDF or IDV

undetectable[28-30]. Frequency of VL assay also depends on many factors, i.e. adherence to ART, accessibility and affordability to VL assay. Adherence to ART should be more closely monitored whenever VL assay is inevitably omitted. Monitoring of $CD4^+$ T-cell count is important because it can be used to evaluate immune restoration after ART and to determine when to stop each OI prophylaxis. Treatment failure should be suspected when absolute $CD4^+$ T-cell count declines more than 30% from prior level.

Adverse effects of ARVs and management

Treatment of HIV-1 infection by ART has become a complicated balance between the benefits of maximum and durable viral suppression and the risks of adverse drug effects. Adverse effects from ARVs cover a broad spectrum and are among the most common reasons for switching or discontinuation of ART[31]. Adverse effects can occur early or late after ART. Some of these effects can impact quality of life of the patients and also their medication adherence. Common adverse effects from ARVs are summarized in Table 6. ARV that cause adverse effect should be substituted by other ARV in the same class if possible. To minimize the risk of subsequent HIV drug resistance, NRTI backbone should be continued for 7-10 days if NNRTI in the same regimen is discontinued due to adverse effect[32]. In a case of severe adverse effects, e.g. lactic acidosis, Stevens-Johnson syndrome, all ARVs should be stopped immediately. Lipodystrophy is one of the most common long-term adverse effects[33-35]. Early switching of causative ARV may avoid irreversible lipodystrophy. Dyslipidemia is common among patients taking PIs, EFV and d4T[36-38]. 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 can manifest as clinical relapse of a previous OI which has resolved after completed therapy, relapse of partially treated OI, unmasking OI which has not been diagnosed, or non-infectious conditions. IRIS has been reported to be associated with several OIs. In Thailand, the major proportion of IRIS are caused by *Mycobacterium tuberculosis*, MAC, and *Cryptococcus neoformans*[39-42]. Clinical manifestations of IRIS mostly appear following the initiation of ART, usually in the first 3 months of therapy. Most patients have low $CD4^+$ T-cell counts prior to ART (usually < 50-100 cells/mm^3). Currently, the pathogenesis of IRIS has not been clearly understood. Due to the nonspecific clinical manifestations, diagnosis of IRIS is usually not straight forward in clinical practice. Physicians must be aware of previous OIs and the association between the time of ART initiation and an increase of $CD4^+$ T-cell count. IRIS should be considered in a differential diagnosis in patients with new clinical manifestations of OIs or clinical deterioration after ART initiation, particularly in patients with advanced HIV disease. Other causes or diseases apart from IRIS should also be considered meticulously in the differential diagnosis; these include worsening of currently treated OI, new infection or morbid condition, adverse effects of ART, or treatment failure with deterioration of HIV infection status. Most patients with IRIS recover within 2-4 weeks and are able to continue ART. Treatment of OI should be administered as indicated. Non steroidal anti-inflammatory drugs or systemic corticosteroids may be given according to the severity of inflammation. Among

Table 6. Adverse effects of ARVs

ARVs	Adverse effects
NRTIs	
AZT	nausea, vomiting, headache, insomnia, asthenia, bone marrow suppression (macrocytic anemia, neutropenia), nail hyperpigmentation
3TC	nausea, vomiting (very rare)
d4T	peripheral neuropathy, lipoatrophy, dyslipidemia, hyperlactatemia and lactic acidosis
ddI	peripheral neuropathy, pancreatitis, nausea, vomiting, hepatitis, hyperlactatemia, lactic acidosis
ABC	hypersensitivity reaction
TDF	renal toxicity, Fanconi syndrome, nephrogenic diabetic insipidus (DI)
FTC	nausea, vomiting, diarrhea, abdominal distension, weakness
NNRTIs	
NVP	rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatotoxicity
EFV	rash, central nervous system symptoms (dizziness, somnolence, insomnia, abnormal dreams, confusion), dyslipidemia, increased transaminase, teratogenicity
PIs	
IDV	nephrolithiasis, nausea, vomiting, indirect hyperbilirubinemia, dyslipidemia, lipodystrophy
RTV	nausea, vomiting, diarrhea, dyslipidemia especially hypertriglyceridemia, lipodystrophy
SQV	nausea, vomiting, diarrhea , headache, dyslipidemia, increased transaminase, lipodystrophy
LPV/r	nausea, vomiting, diarrhea, dyslipidemia especially hypertriglyceridemia, lipodystrophy
ATV	indirect hyperbilirubinemia, prolonged PR interval, 1st degree AV block in some patients, nephrolithaisis
DRV	rash, diarrhea, nausea, headache, increased transaminase

patients who recover from OIs after adequate treatment, repeated antimicrobial therapy for OIs may not be necessary. In case of ongoing maintenance therapy of OI, changing therapy is not needed either.

Diagnosis of treatment failure

Generally, there are 3 categories to define treatment failure: *virological failure*, *immunological failure*, and *clinical failure*. *Virological failure* is the most sensitive and accurate way to diagnose early treatment failure. Plasma VL assay is an important tool. Although virological failure is suspected when VL is > 50 copies/mL, HIV-1 genotype testing can generally be done only when VL is > 1000 copies/mL. Therefore, virological failure is defined as VL > 1000 copies/mL in clinical practice. *Criteria for virological failure* include: VL > 1000 copies/mL after 6 months of receiving ART with good adherence, or a rebound of VL to > 1000 copies/mL in any duration after achieving VL < 50 copies/mL. Patients who have a VL of 51-1000 copies/mL should be reassured the adherence to ART and appointed for repeated VL assay in 2-3 months. *Immunological failure* is considered when there is a decrease or delayed increase of $CD4^+$ T-cell count after ART. However, immunological failure is not sensitive[43]. Patients usually accumulate resistance mutations when immunological failure occurs. Of note, some patients have a decrease or delayed increase of $CD4^+$ T-cell count despite undetectable VL. Changing of ART regimen in these patients are not necessary. *Criteria for immunological failure* include: $CD4^+$ T-cell count increases < 50 cells/mm^3 after a year of ART; absolute $CD4^+$ T-cell count decreases > 30% or percent CD4 decreases > 3% from the highest level previously gained; $CD4^+$ T-cell count decreases to the level lower than pre-ART level. *Clinical failure* is the most delayed method to diagnose treatment failure. Patients usually have virological and immunological failure for a period of time before clinical failure occurs. *Clinical failure* may manifest as clinical relapse of prior OI or occurrence of a new OI. IRIS needs to be excluded before a diagnosis of clinical failure. When diagnosis of treatment failure was done by other criteria apart from virological criterion, HIV-1 VL should be performed to confirm. Early detection of treatment failure, particularly using monitoring of HIV-1 VL, can preserve future options for ART.

ART in patients with treatment failure

Several studies have demonstrated that a high proportion of treatment-experienced patients can achieve a VL level of < 50 copies/mL once again with a proper combination ART, which in general required a minimum of 2 active antiretroviral agents[27,44]. Currently

there are more new classes and more potent ARV in the previous classes. Therefore, the ultimate aim of ART in treatment-experienced patients if feasible is to achieve VL suppression to < 50 copies/mL[27]. When this goal is not achievable, stability of $CD4^+$ T-cell count and clinical status may be maintained for a period of time with selection of the best ART regimen available. Data from recent trials showed no benefit of double-boosted PIs over single-boosted PIs[24, 44,45-48]. Further, pharmacokinetic interactions, tolerance, and long-term adverse effects complicate double-boosted PI therapy. In patients with treatment failure, history of prior ARV exposures should be carefully reviewed. HIV-1 genotype resistance testing should be performed prior to selection of the next ART regimen. If patients have more than one genotype tests, the results of all tests should be reviewed and considered although the latest genotype testing may reveal less or different resistance mutations.

Prior to initiation of the next ART regimen, adherence to ART should be assessed and reassured. If patients have a history of poor adherence in the past, causes of poor adherence should be solved. Currently, treatment failure in Thailand is found in 2 common situations: failing an NNRTI-based regimen and failing a PI-based regimen. In patients failing an initial NNRTI-based regimen with 3TC included in the regimen, NNRTI resistance mutations and M184V/I are commonly observed. Thymidine analog-associated mutations or TAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), K65R, and Q151M are observed in patients with late detection of virological failure, i.e., detection of failure at VL > 4 $\log_{10}$ copies/mL[49,50]. For selecting subsequent therapy in patients failing an initial NNRTI-based regimen, boosted-PI with 2 active NRTIs, indicated by the results of genotype test, should be used for the second ART regimen. Boosted-PI is preferred than non-boosted-PI particularly in patients who have < 2 active NRTIs in the new regimen. 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[51].

Conclusion

Combination ART has become a standard of care with dramatic reductions in morbidity and mortality in HIV-1 infected patients. ART in adults and adolescents should be initiated in all HIV-1 infected patients who meet the inidication. In Thailand, a significant impact of HIV care throughout the country has been evidenced since the implementation of the National Univeral Coverage Program. More initial ART regimens of choice are available. CD4+ T-cell count and VL test as well as genotypic drug resistance test for monitoring of ART are also more accessible in Thailand. The recommendation from these guidelines will be useful for physicians, nurses and other care providers to ensure the proper uses of ART and HIV management. Antiretroviral-related toxicity should be recognized early and properly managed. More imporatantly, adherence to treatment is crucial and has to be emphasized to ensure a long-term success of ART. In case of treatment failure, early recognition and early switch to a proper ART regimen is important and would likely result in successful viral suppression to level of undetectable VL.

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แนวทางการรักษาด้วยยาต้านไวรัสในผู้ใหญ่และเยาวชนที่ติดเชื้อเอชไอวี: ข้อแนะนำของสมาคมโรคเอดส์แห่งประเทศไทย พ.ศ. 2551

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ภูมิหลัง: *ปัจจุบันมีจำนวนผู้ติดเชื้อเอชไอวีมากกว่า 100,000 ราย ที่ได้รับการรักษา ตั้งแต่มีการครอบคลุม การรักษาด้วยยาต้านเอชไอวีในระดับชาติในประเทศไทย แม้ว่าจะมีแนวทางการรักษาในระดับนานาชาติอยู่แล้ว ยังมีความจำเป็นที่จะต้องมีแนวทางการรักษา ที่สามารถนำมาใช้ได้จริงในประเทศไทย*

วัสดุและวิธีการ: *แนวทางการรักษานี้ได้รับการพัฒนาขึ้นโดยคณะผู้เชี่ยวชาญในการดูแลรักษาผู้ติดเชื้อเอชไอวี 17 ราย และทำงานร่วมกันในนามสมาคมโรคเอดส์แห่งประเทศไทย ข้อแนะนำในแนวทางการรักษานี้ได้อ้างอิงจากหลักฐานการศึกษาต่าง ๆ และยาต้านเอชไอวีที่มีอยู่ โดยพิจารณาจากการศึกษาที่สามารถนำมาใช้ได้จริงในประเทศไทยเป็นหลัก*

ผลการศึกษา: *ข้อแนะนำประกอบด้วย การเริ่มการรักษาเมื่อใด ด้วยยาอะไร ติดตามการรักษาอย่างไร ผลข้างเคียงจากยาและการจัดการ การวินิจฉัยภาวะการรักษาล้มเหลว และทางเลือกในการรักษา เมื่อผู้ติดเชื้อมีการรักษาล้มเหลวเกิดขึ้น นอกจากนี้ ยังได้กล่าวถึงการรักษาในสถานการณ์พิเศษ กล่าวคือ เมื่อผู้ติดเชื้อเป็นวัณโรค หรือมีการติดเชื้อไวรัสตับอักเสบชนิดบีร่วมด้วย ระดับเม็ดเลือดขาวซีดีสี่ ที่แนะนำให้เริ่มการรักษาเป็นหัวข้อที่ได้รับการพิจารณาอย่างรอบคอบ และยังคงแนะนำให้เริ่มการรักษา ที่ระดับซีดีสี่ต่ำกว่า 200 เซลล์/ลบ.มม.*

สรุป: *ควรเริ่มการรักษาด้วยยาต้านเอชไอวีในผู้ใหญ่ และเยาวชนที่ติดเชื้อเอชไอวีเมื่อผู้ติดเชื้อมีความเจ็บป่วยที่สัมพันธ์กับการติดเชื้อเอชไอวี เข้าสู่ระยะเอดส์ หรือมีระดับซีดีสี่ต่ำกว่า 200 เซลล์/ลบ.มม. ในผู้ติดเชื้อที่ไม่เคยได้รับยาต้านเอชไอวีมาก่อน แนะนำให้เริ่มการรักษาด้วยสูตรยาที่มียาในกลุ่มเอ็นเอ็นอาร์ทีไอเป็นยาหลัก ควรติดตามระดับซีดีสี่และปริมาณไวรัสของและหนึ่งครั้งต่อปีตามลำดับเป็นอย่างน้อย การจัดการกับปัญหาผลข้างเคียงจากยา และการส่งเสริมให้ผู้ติดเชื้อรับประทานยาอย่างสม่ำเสมอ เป็นปัจจัยสำคัญที่ทำให้ประสบความสำเร็จในการรักษาในระยะยาว*