CHAPTER II
LITERATURE REVIEW

This study was aimed to assess the adherence to ARV medication among HIV-infected/AIDS patients at TAKSIN hospital by using multi-method tool to measure adherence and to analyze the factors affecting patient adherence to ARV medication. The literature review focused on AIDS disease, ARV treatment, adherence to ART, method of assessment adherence and the factors affecting patient adherence to ARV medication.

2.1 Acquired Immunodeficiency Syndrome (AIDS)

2.2 Treatment HIV-infected/AIDS patients

2.3 Adherence to ARV

2.4 Tools of assessing adherence

2.5 The factors affecting patient adherence to ARV medication

2.1 Acquired Immunodeficiency Syndrome (AIDS)

Acquired Immunodeficiency Syndrome (AIDS) is an infectious disease caused by Human Immunodeficiency Virus (HIV). HIV is one of the viral in the retrovirus family, which has two types of the disease identified HIV-1 and HIV-2. The Type 1 (HIV-1) is the major form of infection in HIV/AIDS throughout the world, while the Type 2 (HIV-2) is found mostly in West Africa.[1,2] Transmission of HIV occurs through three primary modes as follows: sexual intercourse, parenteral and perinatal. In sexual intercourse, the receptive anal and vaginal of intercourse are the most common modes of transmission. The probability of HIV transmission from receptive anorectal intercourse was 0.1% to 3% per sexual contact and was 0.1% to 0.2% per sexual contact for receptive vaginal intercourse. Using of contaminated needles or other devices by drug abusers has been the main cause of parenteral transmission of HIV, while, healthcare workers have a small occupational risk of getting HIV. Perinatal infection is the most common cause of pediatric HIV infection. The risk of mother-to-child transmission is approximately 25% in the absence of breast-feeding. Breast-feeding can also transmission HIV.[3] HIV/AIDS patients who have lower immune system or immune deficiency (CD4) would have a high risk to have opportunistic infections (OIs) and also increased morbidity and mortality.[1]

There have been 33 million people living with HIV/AIDS (PLWHA) around the world, 2 million people died from HIV/AIDS worldwide in 2007. Around 2.7 million were newly infected with HIV worldwide in 2007 and WHO reported that only 4 million HIV-positive people had access to ARV medication in low -income and middle-income countries in 2008.[4] The situation of AIDS disease in Thailand that is reported by the Bureau of Epidemiology, the Department of Disease Control[5] showed that there have been 358,260 cases of PLWHA and 95,983 deaths. In Thailand, AIDS is a major health problem, because most of the people living with HIV/AIDS (PLWHA) were 15-59 years old who can yield the productivity to the social.[5]

The HIV life cycle [20]

There are six stages in the HIV life cycle:

1. Binding and Fusion: HIV begins its life cycle when it binds to a CD4 receptor and one of two co-receptors on the surface of a CD4 T-lymphocyte. The virus will fuses with the host cell. After fusion, the virus release RNA and its genetic material, into the host cell.

2. Reverse Transcription: An HIV enzyme called reverse transcriptase converts the single-stranded HIV RNA to double-stranded HIV DNA.

3. Integration: The newly formed HIV DNA enters the host cell's nucleus, an HIV enzyme called integrase "hides" the HIV DNA within the host cell's own DNA. The integrated HIV DNA is called provirus. The provirus may remain inactive for several years, producing few or no new copies of HIV.

4. Transcription: When the host cell receives a signal to become active, the provirus uses a host enzyme called RNA polymerase to create copies of the HIV genomic material, as well as shorter strands of RNA called messenger RNA (mRNA). The mRNA is used as a blueprint to make long chains of HIV proteins.

5. Assembly: An HIV enzyme called protease cuts the long chains of HIV proteins into smaller individual proteins. As the smaller HIV proteins come together with copies of HIV's RNA genetic material, a new virus particle is assembled.

6. Budding: The newly assembled virus pushes out ("buds") from the host cell. During budding, the new virus steals part of the cell's outer envelope. This envelope, which acts as a covering, is studded with protein/sugar combinations called HIV glycoproteins. These HIV glycoproteins are necessary for the virus to bind CD4 and co-receptors. The new copies of HIV can now move on to infect other cells.

Disease classification systems [21]

The U.S Centers for Disease Control and Prevention (CDC) classified HIV/AIDS states based on CD4 cell count and clinical categories which was shown in Table 2.1.

Table 2.1 CDC Classification System for HIV-Infected Adults and Adolescents [21]

CD4 Cell Categories	Clinical Categories		
	(A) Asymptomatic	(B) Symptomatic	(C) AIDS
(1) ≥500 cells/μL	A1	B1	C1
(2) 200-499 cells/μL	A2	B2	C2
(3) <200 cells/μL	A3	B3	C3

CDC Classification System: Category B Symptomatic Conditions [21]

Category B symptomatic conditions refer to symptomatic conditions occurring in an HIV-infected adolescent or adult that meets at least 1 of the following criteria:

a) They are attributed to HIV infection or indicate a defect in cell-mediated immunity.

b) They are considered to have a clinical that is complicated by HIV infection. Examples include, but are not limited to, the following:

1. Bacillary angiomatosis
2. Oropharyngeal candidiasis (thrush)
3. Vulvovaginal candidiasis
4. Pelvic inflammatory disease (PID)
5. Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
6. Hairy leukoplakia
7. Idiopathic thrombocytopenic purpura
8. Constitutional symptoms, such as fever (>38.5°C) or diarrhea lasting >1 month
9. Peripheral neuropathy
10. Herpes zoster (shingles) involving ≥2 episodes or ≥1 dermatome.

CDC Classification System: Category C AIDS-Indicator Conditions [21]

1. There are clinical conditions as follow:
2. Bacterial pneumonia
3. Candidiasis of the bronchi, trachea, or lungs Candidiasis
4. Esophageal
5. Cervical carcinoma
6. Coccidioidomycosis
7. Extrapulmonary
8. Cryptococcosis
9. Extrapulmonary
10. Cryptosporidiosis
11. Chronic intestinal (>1-month duration)
12. Cytomegalovirus disease (other than liver, spleen, or nodes)
13. Encephalopathy
14. Herpes simplex
15. Bronchitis, pneumonitis
16. Esophagitis
17. Histoplasmosis
18. Disseminated or extrapulmonary
19. Isosporiasis
20. Chronic intestinal (>1-month duration)
21. Kaposi sarcoma
22. Lymphoma
23. Burkitt
24. Immunoblastic, or primary central nervous system
25. Mycobacterium avium complex (MAC)
26. Mycobacterium tuberculosis
27. Pulmonary or extrapulmonary
28. Mycobacterium
29. Pneumocystis jiroveci (formerly carinii) pneumonia (PCP)
30. Progressive multifocal leukoencephalopathy (PML)
31. Salmonella septicemia, recurrent (nontyphoid)
32. Toxoplasmosis of brain

33. Wasting syndrome due to HIV (involuntary weight loss >10% of baseline body weight)

34. Chronic diarrhea (≥2 loose stools per day ≥1 month) or chronic weakness and documented fever ≥1 month.

2.2 HIV-infected/AIDS treatment

At present, the standard regimen in the treatment of HIV-infected/AIDS patients is 3 or more combination of antiretroviral drugs which is called "highly active antiretroviral therapy (HAART).[1,6] The combination of antiretroviral therapies for HIV infection have demonstrated efficacy in improving immune function (CD4), reducing HIV viral in plasma (undetectable level), reducing opportunity drug resistance in treatment, improving quality of life and reducing HIV-related morbidity and mortality.[1,7-10]

Antiretroviral therapy (ART) are divided into five class according to [1, 6, 22, 23]

1. Nucleoside reverse transcriptase inhibitors (NRTIs): composes of

Zidovudine (AZT), Stavudine(d4T), Lamivudine(3TC), Didanosine(ddI), Abacavir(ABC), Tenofovir-disoproxil-fumarate(TDF), Emtricitabine(FTC)* and fixed–dose combination: AZT/3TC 300/150 mg, 3TC/ABC, TDF/FTC*, AZT/3TC/ABC*

Mechanism of action: the principle mode of action is inhibition of HIV reverse transcriptase via viral DNA chain termination; inhibits RNA-dependent and DNA-dependent DNA polymerase activities of reverse transcriptase.

2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs): composes of

Nevirapine(NVP), Efavirenz(EFV), Delavirdine(DLV)*, Etravirine(ETV)*and fixed-dose combination of NRTIs and NNRTIs: d4T 30 or 40 mg/3TC 150 mg/NVP 200 mg and AZT 250 mg/3TC 150 mg/NVP 200 mg.

Mechanism of action: activity against HIV-1 by binding to reverse transcriptase. It consequently blocks the RNA-dependent and DNA-dependent DNA polymerase activities including HIV-1 replication .It does not require intracellular phosphorylation for antiviral activity.

3. Protease inhibitors(PIs): composes of

Indinavir(IDV), Ritonavir(RTV), Nelfinavir(NFV), Saquinavir soft gel caps (SQV.Sgc), Lopinavir/ritonavir(LPV/r), Atazanavir(ATV), Forsamprenavir (FPV)*, Darunavir(DRV), Tipranavir(TPV)*.

Mechanism of action: inhibits HIV protease and renders the enzyme incapable of processing polyprotein precursor which leads to production of non-infectious immature HIV particles.

4. Entry inhibitors:

Fusion inhibitor: Enfuvirtide(T-20) (subcutaneously) is the drug that inhibit HIV viral to go in cell.

CCR5 antagonist: maraviroc(MAL)*

5. Integrase inhibitors: Raltegravir(RAL)*

(* not available in Thailand)

The primary goals driving the decision to initiate antiretroviral therapy [1, 6, 23] are to

1.) Reduce HIV-related morbidity and prolong survival.

2.) Improve quality of life (QOL).

3.) Restore and preserve immunologic function, increase CD4.

4.) Maximally and durably suppress viral load (reduce HIV viral in plasma undetectable level).

5.) Prevent vertical HIV transmission.

Adoption of treatment strategies recommended in these guidelines has resulted in substantial reductions in HIV-related morbidity and mortality and has reduced vertical transmission. Higher plasma HIV RNA levels (viral load) are associated with more rapid disease progression, although other factors likely contribute as well to the rate of CD4 T-cell decline. Maximal suppression of plasma viremia for as long as possible to delay the selection of drug resistance mutations, to preserve CD4 T-cell numbers, and to confer substantial clinical benefits are the most important goals of antiretroviral therapy.[1, 6, 23]

Recommendation for initiation of ART

The details in table 2.2, table 2.3 and table 2.4 are the recommendation for initiation of antiretroviral therapy (ART) of THAILAND Guideline, WHO Guideline and Department of Health and Human Services (DHHS) Guideline, respectively.

Table 2.2 THAILAND Guideline as follow: [23]

Clinical symptom	CD4 (cell/mm^3)	Recommendation
AIDS-defining illness	Value anything	Treatment with ARV
Symptomatic HIV disease	Value anything	Treatment with ARV
Asymptomatic HIV disease	<200	Treatment with ARV
Asymptomatic HIV disease	200-350	Follow clinical symptom, CD4 every 3 month , move treatment
Asymptomatic HIV disease	>350	Follow clinical symptom, CD4 every 6 month , move treatment

Table 2.3 WHO Guideline for start antiretroviral therapy in HIV-Infected Adults and Adolescents [1]

CD4(cells/mm^3)	Recommendation in Treatment
< 200	Treatment with ARV
200-350	Treatment with ARV prior CD4 will reduce to < 200 cells/ mm^3
> 350	No treatment

Table 2.4 Department of Health and Human Services (DHHS) Guideline for start antiretroviral therapy in HIV-Infected Adults and Adolescents in United States [1]

Clinical Category	CD4(cells/μL)	Plasma HIV RNA (copies/ml)	Recomendation in Treatment
AIDS defining illness	Any value	Any value	Treat with ARV
Asymptomatic HIV disease	CD4< 200	Any value	Treat with ARV
Asymptomatic HIV disease	CD4>200 but≤350	Any value	Should treat with ARV and should explain advantage and disadvantage of ARV treatment
Asymptomatic HIV disease	CD4>350	>100,000	Some physician recommend to treat with ARV
Asymptomatic HIV disease	CD4>350	<100,000	May start ARV

Guideline for selection regimen for the patients who are naive for antiretroviral therapy in THAILAND Guideline [1,23]

1. **First regimen**: The standard regimen for Thai HIV/AIDS patients is stavudine+lamivudine+nevirapine(GPOvir)
2. **Second regimen**: There are three alternative regimens:

2.1 stavudine+lamivudine+efavirenz is recommended when patients experience to NVP side effects such as allergic.

2.2 zidovudine+lamivudine+nevirapine is recommended when patients have an adverse drug reaction related to stavudine.

2.3 zidovudine+lamivudine+efavirenz is recommended when patients have an adverse drug reaction or allergy related to stavudine and nevirapine.

3. **Third regimen:** There are two alternative regimens:

3.1 Stavudine+lamivudine+indinavir/ritonavir or

3.2 Zidovudine+lamivudine+indinavir/ritonavir

WHO Guidelines [1]

WHO Guidelines recommended that the **first regimen** should be 2NRTIs+NNRTIs and **second regimen** should be 2NRTIs+PIs.

1. NRTIs group type 1: should select between lamivudine and emtricitabine
2. NRTIs group type 2: should select between zidovudine and stavudine or tenofovir and abacavir
3. NNRTIs group: should select between efavirenz and nevirapine

(For the PIs group WHO recommends the second regimen)

DHHS Guideline [1]

Table 2.5 Antiretroviral therapy regimen that is recommended as the preferred component in naive antiretroviral therapy by the Department of Health and Human Services (DHHS), United States

	Column A (NNRTI or PI)		Column B (NRTI 2 type)
Preferred component	NNRTI or PI Efavirenz ATZ+RTV Fosamprenavir+RTV (2 times/day) LPV+RTV (2 times/day)	+	Tenofovir + Emtricitabine or Zidovudine + Lamivudine
Alternative to Preferred component	NNRTI or PI Nevirapine ATZ Fosamprenavir Fosamprenavir+RTV (1 time/day) LPV+RTV (1time/day)	+	Abacavir + Lamivudine or Didanosine+(Emtricitabine or Lamivudine)

Significant drug interactions can occur with many antiretroviral agents: [3]

1. **Ritonavir** is a potent inhibitor of cytochrome P450 enzyme 3A and is used to reduce clearance of other PIs.
2. Two NRTIs, **zidovudine** and **stavudine**, antagonize each other's metabolism and should not be given together.
3. Rifampin may reduce the concentrations of PIs and is contraindicated with use of most PIs.
4. Saint John's wart is a potent inducer of metabolism and is contraindicated with PIs and NNRTIs.

Causes of Antiretroviral Treatment Failure [1, 6, 23]

Antiretroviral Treatment Failure refers to suboptimal response to therapy. Treatment Failure is often associated with Virologic Failure, Immunologic Failure, and/or Clinical progression. Many factors are associated with increasing risk of Treatment Failure, as follow:

1. Baseline of the patients , such as:
    a. Previous initial introduction to therapy, which less potent regimens
    b. Higher pre-treatment of baseline HIV RNA level
    c. Lower pre-treatment CD4 T-cell count
    d. Prior AIDS diagnosis
    e. Co-morbidities (e.g., depression, active substance use)
    f. Presence of a drug-resistant virus
    g. Prior treatment failure with the development of drug resistance or cross resistance
2. Incomplete medication adherence (non-adherence) and missed clinic appointments
3. Drug side effects and toxicity
4. Suboptimal pharmacokinetics (absorption, metabolism and food/fasting requirements, adverse drug-drug interactions)
5. Suboptimal potency of the antiretroviral regimen
6. Other, unknown reasons

2.3 Adherence to ARV

The Ministry of Public Health in Thailand defines adherence as taking medicine correctly (correct type, correct dose, correct course, correct time) taking medicine on time (variance should not exceed than half an hour) taking medicine always (take medicine on time everyday) and taking medicine continuously (continually forever) by the patients who can participate and decide for their treatment.[16]

Bosworth, Steffens, Flint and others defines adherence as the patient's participation and engagement in maintaining regimen as follows: she or he believes treatment will be beneficial, strongly implying a therapeutic partnership between provider and patient that is essential for the patient's success in following the prescribed regimen.[24]

The U.S. DHHS defines adherence as closely monitoring or adhering to a prescribed treatment regimen. This includes taking the correct dose at the correct time, exactly as prescribed.[2]

Adherence to ARV medication is a factor for treatment successful. A level of adherence more than or equal to 95% of prescribed doses is need for a maximal response to ARV medication (undetectable viral load). Conversely; suboptimal intake of antiretroviral therapy will decrease the probability of viral suppression and it may increase of drug-resistant HIV-1 strains.[1, 6, 13, 25]

The results of the studied of Wagels by using MEMS (medication event monitoring system) to assess the adherence during the first month to six month of treatment showed that good adherence (>95% doses took) associated with viral suppression and adherence level > 95% from first month of ART will significantly higher suppression when compared to patients with lower adherence rates.[27]

The results of the studied of Abaasa, Kalyango, Levin and others by using self-report and pill count found that 78.2% of patients had mean adherence > 95% and had 42.5 deaths per 100 patient-years for non-adherence patients and 6.1 deaths per 100 patient-years for adherence patients. Non-adherence to ART was significantly associated with mortality. Patients that had a CD4 count < 50 cells/mm3 will have a higher mortality when compared to patients with a CD4 count equal to or more than 50 cells/mm3 and good adherence will improve survival.[28]

The results of the study of Paterson, Swindells, Mohr and others that explored the effects of different levels of adherence of therapy to virologic outcome,

immunologic outcome and a clinical outcome showed that adherence was significantly associated with a successful virologic outcome and will increase CD4 and virologic failure. The samples in this study was 22% of patients with an adherence of 95% or greater, 61% of patients with (80% - 94.9% adherence), and 80% of patients with less than 80% adherence. Patients with adherence of 95% or greater had fewer days in the hospital (2.6 days per 1000 days of follow-up) than patients with less than 95% adherence (12.9 days per 1000 days of follow-up). No opportunistic infections or deaths happen in patients with 95% or greater adherence.[13]

Those related studies of adherence to antiretroviral found that good adherence (more than or equal 95 percent) will affect to the suppression of RNA, increase CD4 and prolong survival and reduce morbidity as showed in Table 2.6

Table 2.6 Related studies of adherence

Authors/year	Objective	Results	Conclusion
Wagels,2004	to evaluated adherence by using MEMS during the first 25 days of treatment and week 24 of program	Adherence level >95% in the first 4 weeks can improve viral suppression (77% of patients was suppression viral load at adherence >95%)	higher suppression RNA during the first month are associated with good adherence or >95%
Abaasa,et al 2008	to assess adherence by self-report, pill count	78.2% of patients >95% adherence, 6.1 deaths per 100 patient-years for adherence, CD4 count of less than 50 cells/mm3 will have a higher mortality	good adherence will improve survival

Paterson,et al 2000	to explored effects of different levels of adherence of therapy on virologic outcome, immunologic outcome and a clinical outcome	Adherence associated with increase CD4, Virologic failure was 22% of pts (95% adherence) , 61% of pts.(80% - 94.9% adherence), 80% of pts.(< 80% adherence). 95% adherence had fewer days in the hospital (2.6 days per 1000 days), < 95% adherence (12.9 days per 1000 days). No OIs or deaths happen in patients with 95% adherence	adherence was associated with a successful virologic outcome, immunologic outcome and a clinical outcome

2.4 Tools of assessing adherence

Tools for adherence assessment [1, 15, 30] can be divided into two categories as follow:

1. Direct and objective measures as follow:

-Directly observed treatment (DOT)

-Therapeutic drug monitoring (TDM)

-Biomarkers

-Medication event monitoring system (MEMS)

2. Indirect measures as follow:

-Pharmacy records

-Self-report

-Pill count (PC)

-Visual analogue scale (VAS)

-Pill identification test (PIT)

Directly observed treatment (DOT): the technique of this method is that the healthcare provider will direct administer medication to patient and observe the patient in taking medicine at the moment.[31] However, Farmer, Leandre, Mukherjee and others recommended that DOT was more expensive.[32]

Therapeutic drug monitoring (TDM): the technique of this method is to monitor the therapeutic drug levels in blood, however, TDM have some limitations. First, TDM can only monitor the adherence to the dose prior the clinic visit. Second,

the pharmacokinetics of many antiretroviral, especially protease inhibitors, may be affected from drug–drug interactions, drug interactions with foods and nutritional supplements that can affect to the potential poor absorption, for example, Ritonavir has drug interactions and auto induces its own metabolism. Third,[33] this method is more expensive.

Biomarkers: this method can be used to monitor adherence by adding the second non-toxic medicine in order to indicate that patient took medication such as add Vitamin B2 to check the level of vitamin B2 in the urine.

Medication Event monitoring System (MEMS): MEMS is an Electronic pill bottle, it is a new method to measure adherence. This device composes of special pill bottle caps equipped with have an electronic chip and hardware that record each time that patient opens a pill bottle. Patients who use pillboxes may open their electronic bottles only daily or weekly (to fill their pillboxes). However, electronically measured adherence may not be accurately measured because opening the cover of drug bottle but not taking a pill that it cannot confirm that medicine be took. Finally, the cost of MEMS is more expensive.[33] However MEMS are correlate with virological outcome.

Pharmacy records: this method is a convenient measurement of adherence in the situation that the patients get ART from only one source. However, when a patient receives drug from pharmacy, it is not sure that ARV pills have been taken or not.

Self-report: this method is the most common tool to measure the adherence. This method use face-to-face interviewing and ask the patient to complete the questionnaires. In face-to-face interviewing, the patients were asked about the number of dose that they miss during the past 7 day.[30] The part of patient-completed questionnaire is designed to evaluate a patient's treatment adherence behavior. There is many versions of self-report such as Patient Medication Adherence Questionnaire (PMAQ) that contains 31 items [34], Simplified Medication Adherence Questionnaire (SMAQ) that contains 6 items [8]. Self-report is the simplest tools to measure adherence with speedy and viability to use. However, the adherence data from this method may be overestimated and patients may give data that are not really true. However, several studies highlighted the usefulness of the self-report as an adherence measurement tool, and showed that it correlate with the virological outcome. It shows adequate levels of sensitivity and specificity when it was compared with other measures. It is reliable, showing sufficient internal consistency

and reproducibility. It is easy to apply and inexpensive. Self report is an instrument that may be used in the majority of clinical settings.[8]

Pill count (PC): the technique of this method is to count the amount of drug remaining. This method is very easy, convenient but data is unreliable because patients may leave the pills without taking them.[30]

Visual analogue scale (VAS): the technique of this method is to ask the patients to rate about their behavior of adherence to the prescribed ART from 0 (non adhere) to 10 (adhere). The meaning of 10 score is that he or she took all medicine doses and the 0 score is that he or she missed all doses. VAS is a simple tool.[15]

Pill identification test (PIT): this method is a new tool to measure adherence, the healthcare provider will ask the patients about the name of medicine, number of pills per dose, time to take pill and other instructions. PIT is reliable and correlate with validated self-report adherence measure.[15]

Even though, some adherence tools are valid, majority of tools cannot meet all the features of ideal tool. At present, there is no gold standard in measurement of adherence. WHO recommended multi-method adherence tool to be used in measuring adherence. Multi-method adherence tool is an accurate assessment adherence which is necessary for effective and efficient treatment planning.[35]

In this study, multi-method tools were used including self-report, VAS, PIT, and pill count based on the studied of Steel, Nwokike, Joshi and others.[15] Multi-method tool to measure ART adherence in resource-constrained settings was developed by Rational Pharmaceutical Management Plus Program, Management Sciences for Health, supported by U.S.Agency for International Development (USAID).

2.5 The factors affecting patient adherence to ARV medication

For HIV-infected/AIDS patients, a good adherence (equal or more than 95% of the prescribed dose) is associated with HIV viral suppression.[13] The results of Hogg, Yip, Chan and others study revealed that every 10 percent decrease in adherence will increase 16 percent of HIV-related mortality.[14] this finding was confirmed by the results of Chesney study [17] and the American Pharmacists Association study.[18]

Golin, Liu, Hays and others [41] explored 140 HIV-infected patients at a county hospital HIV clinic during the year follow the initiation of a new highly active

ARV regimen. The purpose of this study was to access the predictors of long-term (up to 1 year) adherence to newly initiated combination ARV. Measurement for adherence was done every 4 weeks by calculation score from medication event monitoring system (MEMS), pill counts and self-reports and evaluated demographic. The result showed that by average, patients took 71% of their prescribed dose. African-American ethnicity, lower income, lower education, higher alcohol use, higher dosage frequency, and fewer adherence aids (e.g. pillbox, timer) were associated with poorer adherence level.

Pinheiro, Carvalho-Leite, Drachler and others [48] conducted a cross-sectional study in HIV-infected adults treated with ARV in Southern Brazil. Adherence to treatment was assessed by a self-report. The results showed that of the 195 patients, 56.9% reported ≥95% adherence on the previous two days. An adherence increased with the self-efficacy in taking medicine and decreased with perceptive of negative effects and physical concerns. An adherence was lower for taking ARV >4 times per day and was higher for the patient with at least 8 years of schooling. Taking medicine >4 times a day were independently associated with non adherence. Self-efficacy was the most important factor to predict the adherence. The number of years of schooling was positively associated with adherence.

Glass, De Geest, Weber and others [49] conducted a cohort study and used 2-item self-reported adherence questionnaire to measure adherence. The definitions of non-adherence in this study are missing 1≥ dose, or missing ≥ 2 doses and taking medicine <95% of dose in the previous 4 weeks. The results showed that > 30% of patients reported missing ≥ 1 dose, 14.9% missed ≥ 2 doses, and 7.1% took < 95% of doses in the previous 4 weeks and the patients who are young, living alone, the number of regimens, were the factors associated with non-adherence. In conclusion, this studied found that the younger patients, lacked of social support and the perception of the complexity of treatment were important factors that related to non-adherence with ARV.

Maggiolo, Ripamonti, Arici and others [50] conducted cross-sectional study on HIV patients that receive HAART from January to May 2001 to assess the adherence by using a self-administered questionnaire. The purpose of this studied was to assess the factors associated with lower compliance and causes of non-adherence. The results showed that 50.9% of patients were adherence and the results of multiple logistic regressions showed that older, lower numbers of pills, fewer daily

doses were factors associated with adherence behavior and forgetful, being away from home and problem with ARV schedule were the most frequent causes of non-adherence.

Murri, Marconi, Wu AW, and others [51] conducted a study to assess variables that can predict the non-adherence. The method of this studied was a prospective study of HIV-infected patients who were prescribed Ritonavir-or Indinavir-containing regimen by using a questionnaire and assessed the patients' knowledge of the treatment regimen, adherence behavior, and reason of missing ARV. Non-adherence was measured by self-report. The results showed that age less than 35 years old, and having adverse effect "a lot" of vomiting or pruritus was significantly correlated to non-adherence. In conclusion, it was found that younger age and self-reported vomiting or pruritus was associated with non-adherence.

Duran, Spire, Raffi and others [9] conducted a study to assess self-reported symptoms in the patients who started to take two nucleoside reverse transcriptase inhibitors and one PIs and assessed the influence of these symptoms on adherence. The adherence and the patient reported symptoms were measured at 1 and 4 months after initiation to HAART through self-administered questionnaires. Results showed that the patients had at least one symptom of fatigue or diarrhea (94.0% at Month 1; 88.0% at Month 4). These symptoms were the most common side effects that were reported. About 81.3% and 75.0% of patient adhered to HAART during the 4 days prior to M1 and M4, respectively. Younger, history of antiretroviral treatment, unstable housing, poor social support, alcohol consumption, and the patients who reported a higher number of symptoms at M1 were more likely to be non adherent at M4. In conclusion, it was found that patients with a high number of symptoms after HAART initiation were high risk of non-adherence.

Murphy, Belzer, Durako and others [38] conducted a study to find the barriers to HAART adherence among HIV-infected adolescents and to explore the association of barrier and non-adherence. The findings showed that viral load was significantly associated with self-reported adherence, only 28.3% of adolescents reported taking all of their prescribed ARV. The barriers to adherence were medication-related ADR and complications in daily routine.

Schneider, Kaplan, Greenfield and others [53] conducted a study to assess the association of physician-patient relationship and adherence. The adherence was measured by using a 4-item self-report scale. The physician-patient relationship was

measured in the area of general communication, HIV-specific information, participatory decision making, overall satisfaction, willingness to recommend physician, and physician trust. The results showed that the patients were 42 years old, 15% were female, 73% were white, and 57% were gay, physician-patient relationship was significantly associated with adherence. In conclusion, this studied showed that the physician-patient relationship was associated with medication adherence and the researchers suggested that physician-patient relationship is an important point of intervention to improve patients' medication adherence.

In Thailand, Kamolrat Inthisak [54] conducted a study to assessed adherence to ARV and explored the factors affecting an adherence to ARV at Chiangmai Hospital, Nongkai. Samples were 21 patients who received ARV during April to June 2007. Adherence was assessed using a visual analog scale, pill counts and medication logbook. The result from the visual analog scale showed that there was 81.6% adherence and 61.9% adherence during 7 day and 1 month respectively, and confirmed by pill count and log book indicated that over 90% of patients had >95% adherence. Factors affecting adherence were age, marriage status, occupation, communication skills of health care professionals, numbers of drugs prescribed.

Kanitta Punsreniramon [40] explored cross-sectional and studied to medical adherence by using tools as follow: pill count, GEEMA questionnaire and medication taking diary and studied factors influence patients adherence and studied relationship between medication adherence. The results found that adherence level were 91%, 95.5% and 97% assessment by GEEMA, medication-taking diary, pill count respective. Correlation analysis using score from GEEMA in order to seek factor affect medical adherence and found that age, alcohol, knowledge of disease and medicine, self efficacy, income, social support and healthcare team-patient.

Thidaporn Jirawattanapisal, Opart Karnkawingpong, Ponlasin Narkwichienet and others [55] explored accuracy and compare four different tools consist of pill count, interview, VAS, medical reminder card in monitor adherence among HIV-infected patient in Thailand. The results found that from four tools, there was 90.7% of patient adherence $\geq$ 95% adherence. Combine of result from four tools had better correlation with HIV viral load than using only one tool.

Those related studies are following Table 2.7

Table 2.7 Related studies of factor affecting adherence

Authors/ year	Objective	Studied sample	Adherence measurement	adherence	Factor associated with adherence
Golin, et al 2002	to access predictor of long-term adherence to new initiated ARV	140 cases	MEMS, pill counts, self-report	71% that adherence >95%	ethnicity, lower income, lower education, higher alcohol use, higher dose frequency, fewer adherence aids were poor adherence
Pinheiro, et al 2002	to access HIV-infected being treat with ARV and factors of adherence	195 cases	self-report	56.9% that adherence >95%	self-efficacy, low dose frequency, number of years of school > 8 yrs were adherence
Glass, et al 2006	to explored HIV –infected by cohort study and factor influence to adherence	3,607 cases	self-report	93% that adherence>95 %	younger, lacked social support were non adherence
Maggiolo , et al 2002	to assess the factors associated with non adherence and cause of non adherence	623 cases	self-report	50.9% that adherence >95%	older, lower number of pills, fewer daily doses were adherence
Murri, et al 2001	to assess variables that predictive of non adherence	140 cases	self-report	69% that adherence >95%	younger, vomit and pruritus were non adherence
Duran, et al 2001	to assess the influence of these symptom to adherence	336 cases	self-report	75% that adherence >95%	high number of adverse symptom was non adherence

Authors/ year	Objective	Studied sample	Adherence measurement	adherence	Factor associated with adherence
Murphy, et al 2003	to assess the barriers to ARV in adolescent	231 cases	self-report	28.3% that adherence >95%	ADR, complication in daily routine were non adherence
Schneider, et al 2004	to assess of a better physician-patient relationship to adherence	554 cases	self-report	87% that adherence >95%	better physician-patient associated to adherence
Inthisak, 2008	to assess adherence to ARV and explore the factor affect adherence	21 cases	VAS, pill counts, medication logbook	61.9% that adherence >95%	age, marriage, occupation, communication skill of health care professional, clarify data, sufficient drug supply, number of drug item and ease of oral administration
Punsrenir amon, 2006	to assess adherence by using many tools and factors influence adherence and relationship between medication adherence and stage of change	276 cases	pill count, self-report and medication taking diary	91.7% ,95.5%, 97.3% respective	age, alcohol, knowledge of disease and medicine, self-efficacy, income, social support, healthcare term-patient

Authors/ year	Objective	Studied sample	Adherence measurement	adherence	Factor associated with adherence
Turner BJ,2003	to evaluate the factor relationship with adherence	3,249 cases	self-report	82% that adherence> 95%	women have fewer adherence
Howard A.A, 2002	to determine the predict of adherence over time take ARV	161 cases	MEMS	88% that adherence >95%	more than 2 years were adherence

The results in Table 2.7 showed that from thirteen studies, there were eight studies used only self-report for measure adherence, there was one study used MEMS for measure adherence, there were three studies used three tools for measure adherence such as 1) MEMS (medication event monitoring system), pill counts, self-report. 2) VAS, pill counts, medication logbook. 3) Pill counts, self-report, medication taking diary. There was one study used four tools for measure adherence such as pill counts, interview, VAS, medical reminder card. This study used multi-method for measurement the patients' adherence. WHO recommended that it should be an accurate assessment, because adherence tool is necessary for effective and efficient treatment planning. Only one tool may not be valid and may not have high accuracy. This study used the measurement about adherence assessment by tools from the study of Steel, Nwokike, Joshi and others [15] in measurement adherence including Self-report, Visual analogue scale (VAS), Pill Identification Test (PIT), Pill count.

The results from table 2.7 showed that factors associated with adherence were:

1. Patient –related Factors

Gender

The result of Turner [36] studied found that women have fewer adherences than men. The Studied of Littlewood, Vanable, Carey and others [37] found that women have scored higher adherences than men.

Age

The study of Murphy, Belzer, Durako and others [38] found that only 28.3% of adolescents taking all of their prescribed antiretroviral medications in the previous month. Kamolrat Inthisak studied found that younger effect to more than 95% adherence.[19] Glass, De Geest, Weber and others[49] Murri, Marconi, Wu and others[51] found that younger were non adherence.

Knowledge of disease and medication

Kanitta Punsreniramon studied[40] found that Knowledge regarding the disease and antiretroviral therapy on the part of patients knowledge in disease and antiretroviral therapy were associated with adherence in antiretroviral therapy.

Self-efficacy

Golin, Liu, Hays and others [41] found that the patient's good faith and self-efficacy in took antiretroviral medication will increase adherence. Kanitta Punsreniramon studied found that self-efficacy effect to adherence.[40]

Income

Golin, Liu, Hays and others [41] Kanitta Punsreniramon[40] found that lower income were poor adherence.

Education

Golin, Liu, Hays and others[41] Pinheiro, Carvalho-Leite, Drachler and others[48] Thidaporn Jirawattanapisal, Opart Karnkawingpong, Ponlasin Narkwichienet and others[55] found that lower education were poor adherence.

Status

Kamolrat Inthisak[54] found that married were high adherence.

Occupation

Thidaporn Jirawattanapisal, Opart Karnkawingpong, Ponlasin Narkwichienet and others [55] found that had occupation were high adherence.

2. Treatment-related Factors

Adverse effects

Murri, Marconi, Wu and others found that vomit and pruritus were associated with non adherence.[51] Duran, Spire, Raffi and others found that high number of adverse symptom was associated with non adherence.[9] Murhy, Belzer, Durako and others[38] found that ADR were associated with non adherence.

Dose frequency

Golin, Liu, Hays and others [41] Murphy, Belzer, Durako and others [38] Pinheiro, Carvalho-Leite, Drachler and others [48] found that a greater dose frequency was associated with a lower adherence level (p=0.006). However, the total number of pills and the number of antiretroviral medications were not significantly associated with adherence.

Duration of treatment

Howard studied found that the length of time on the prescribed medication that patients on antiretroviral therapy for more than 2 years will have an adherence level more than patients on antiretroviral therapy of 2 years or less than 2 years (p=0.005).[44]

3. Health care team-related Factors

Patient-healthcare provider relationship

A good patient-healthcare provider relationship may be important motivate for took pill and adherence to complex combination drug therapy.[40] Schneider, Kaplan, Greenfield and others[53] found that best physician-patient relationship to adherence.

4. Social or family support

Several studied found that satisfaction with one's social support improved good adherence and non-adherence reported that will less satisfaction with their social support therefore low social support are associated with poor adherence to ART.[40, 49]