ORIGINAL ARTICLE

Virological Outcome in Newly Adult HIV Cases on Rapid ART initiation in Thailand, A Retrospective Study

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Background: Same day or rapid ART initiation was suitable for asymptomatic HIV stage. Studies have shown benefits in faster virological suppression and reduction of loss to follow up rate.

Objective: To compare virological outcome at 24 and 72 weeks in adult HIV infection starting ART within two weeks as the rapid ART group, or more than two weeks as the standard care group.

Materials and Methods: A retrospective cohort study was conducted at Chiangrai Prachanukroh Hospital, Chiangrai, Thailand. All new cases of patients diagnosed with HIV infection between October 1, 2012 and September 30, 2019 were included. The study included demographic data and virological outcome at 24 weeks and 72 weeks, status of loss to follow up or death.

Results: One thousand seven new adult HIV cases were reviewed. Mean age was 34.03±11.27 years old. Male was predominant at 70.51%, mode of transmission was heterosexual at 87.49%. Median CD4 of cases was 268 cells/mm^3. Of all the cases. 36.6% of cases were prescribed ART within 14 days with a median of eight days. NNRTI base regimen was given in 93.64% of the cases. Virological suppression less than 40 copies/mL at 24 weeks was 84.94% in rapid ART group compared with 82.92% in standard group. There was no statistical difference between the groups (p=0.747). Virological suppression less than 40 copies/mL at 72 weeks was 97.14% in rapid ART group compared with 93.84% in standard group, with no statistical difference (p=0.079). Retention to care was higher in rapid ART groups (p=0.012) and mortality rate was lower in rapid ART group (p=0.003). Loss to follow up rate was not different between the groups.

Conclusion: There was no differences in virological outcome and loss to follow up between the rapid ART and standard groups, but there was better retention to care and lower mortality rate in the rapid ART group.

Keywords: Adult; HIV; Rapid ART; Virological outcome; LTFU; Thailand

Received 10 October 2022 | Revised 5 December 2022 | Accepted 14 December 2022

J Med Assoc Thai 2023;106(2):146-53

Website: http://www.jmatonline.com

The highly active antiretroviral therapy (HAART) improved the treatment of the human immunodeficiency virus (HIV) infection epidemic worldwide[1]. HAART increased survival and decreased mortality in people living with HIV (PLWH)[2]. In 2017, the World Health Organization (WHO) recommended the rapid initiation of antiretroviral therapy (ART) on the same day HIV infection was diagnosed[3-6]. The duration of the same day or rapid ART treatment was within one to seven days of HIV diagnosis[7,8]. The rapid initiation of ART improved the virological outcome in virus undetectable for decreased transmission and better retention of HIV patients[3,9-12].

Various studies revealed better outcomes of rapid ART treatment. In the United States, 94.9% of rapid initiation of ART within 24 hours after diagnosis of HIV infection had significantly faster virological suppression compared to universal ART, which had median times of viral suppression of 1.8 and 4.3 months, respectively (p<0.001), and only 10.3% loss to follow-up (LTFU)[8]. In Thailand, there were favorable outcomes in virological suppression after scaling up rapid ART. The LTFU or death in the ART initiation within one month in youth living with HIV (YLHIV) in 2014 to 2018 revealed the cumulative incidence was only 3.8% (95% CI 3.6 to 4.1) in the first period and 1.9% (95% CI 1.8 to 2.1) in the second period after scaling up rapid ART initiation[13]. The rapid treatment of HIV infection on the same day or within 14 days of HIV infection diagnosis improved

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How to cite this article:

Khusuwan S, Sirijanchune P, Pongprapass S. Virological Outcome in Newly Adult HIV Cases on Rapid ART initiation in Thailand, A Retrospective Study. J Med Assoc Thai 2023;106:146-53.

DOI: 10.35755/jmedassocthai.2023.02.13774

the time to virological suppression safely[4,8]. Currently, the WHO recommendation of same-day ART ranges from same day to seven days after HIV was diagnosed for improved favorable outcomes in virological suppression and health optimization response[7,14]. Recent trials of starting ART as soon as possible demonstrated great benefits[15,16]. So, various studies strongly recommended rapid initiation of ART for improving overall health status[17,18].

In contrast with the same-day initiation (SDI) of ART in South Africa, the SDI between 2017 and 2018 in Johannesburg and Mopani Districts revealed the overall rate of SDI was 40.4%. The LTFU was high at 30.1% compared to 22.4%, 19.8%, and 21.9% in the groups among those who started ART in 1 to 7 days, 8 to 21 days, and 22 days or later, after HIV diagnosis, respectively ($p<0.001$)[19]. Routinely, the present study hospital starts rapid ART within a median average of ten days after HIV infection was diagnosed. Some newly diagnosed HIV patients delayed the ART treatment due to various factors. The optimized time for ART initiation would be warranted for evaluation. The purpose of the present study was to determine the impact of ART initiating time. The present study aimed to evaluate the timing of treatment outcomes from rapid ART initiation compared to standard usual care in newly HIV-diagnosed patients.

Materials and Methods

Study design

A retrospective review of individuals' medical records of newly diagnosed HIV patients between October 1, 2012, and September 30, 2019 was done. Patients have been prescribed the ART on the same day or within two weeks of their initial clinical visit to the ART clinic were in the Rapid ART group, while the patients that have been prescribed the ART after more than 2 weeks of diagnosis were in the Standard ART group. The study aimed to evaluate the efficacy of rapid ART compared to standard ART treatment in virological outcomes at 24 and 72 weeks. Thailand's National Guidelines on HIV/AIDS Treatment and Prevention recommends to measure the RNA HIV viral load (VL) after 24 weeks of treatment, followed by monitoring yearly if HIV VL was undetectable. The present study followed up on the HIV VL of the patients after initial treatment at 24 and 72 weeks. The present study was conducted at the ART outpatient clinic, Chiangrai Prachanukroh Hospital. The study protocol was approved by the Ethics Committee in Human Research Chiangrai Prachanukroh Hospital (EC CRH 094/61IN) and was carried out following the Declaration of Helsinki. Consent waiver was obtained for the retrospective study.

Participants

The present study included all newly diagnosed HIV patients being initiated on ART between October 1, 2012 and September 30, 2019, at Chiangrai Prachanukroh Hospital. The HIV patients diagnosed in other hospitals and aged below 18 years were excluded. The patients had tested HIV positive with the fourth-generation HIV antibody followed by the confirmation test of two different companies of immunochromatography assay. The patients were divided into two groups classified by the time ART was initiated. In the Rapid ART group, the patients started ART on the same day or within two weeks. The Standard ART group had initiated ART more than two weeks after diagnosis.

Assay

The HIV testing method for diagnosis used reactive immunoassay of HIV antibody assay followed by two different companies of immunochromatography test. Thailand's National Guidelines on HIV/AIDS Treatment and Prevention recommend measuring the RNA HIV VL after 24 weeks of treatment, followed by yearly HIV VL testing if VL was undetectable.

Outcome

The primary outcome was to monitor the HIV VL 24 weeks after ART initiation. After the HIV VL was undetectable, the HIV VL was monitored annually. The secondary outcome of the present study was to determine the HIV VL after ART treatment at 72 weeks. The HIV viral suppression was defined as the VL below 40 copies/mL. The LTFU was defined as the patient had not visited the clinic for six months after the last appointment.

Statistical analysis

Descriptive statistics were used. These data were presented by frequency, percentage, mean, median, standard deviation (SD), 95% confidence interval (CI), and p-value. The baseline characteristics were compared using exact probability tests for categorical variables; Student's t-test or Wilcoxon rank-sum test was used to comparing the mean difference of continuous variables. Mean together with SD were used to describe normally distributed continuous variables, while median and interquartile range

(IQR) were used to describe non-normally distributed continuous variables. Univariable and multivariable regression analyses were used to evaluate the HIV treatment between intervention groups. All statistical analyses were two-tailed. A p-value of 0.05 was considered statistically significant.

Results

One thousand seven newly diagnosed HIV patients between October 1, 2012 and September 30, 2019 were included in the present study. The patients who did not have health insurance coverage, without the national AIDS program number were excluded. Their baseline characteristics are shown in Table 1. The mean age was 34.03±11.27 years. The newly diagnosed male HIV patients were predominant of the participants with 70.5%. The mode of infection was heterosexual transmission in 87% of all patients. The median CD4 (IQR) level was 268 (50 to 318) cells/mm³. There were 12.4% of hepatitis B (HBV) coinfection and 5.3% of hepatitis C (HCV) coinfection. The sexually transmitted disease with syphilis coinfection was 7.5%. The present study showed 56.21% of the patients were in the asymptomatic stage at the initiation of ART treatment, 35.35% of the patients had opportunistic infection (OI) with tuberculosis (30.9%), pneumocystis pneumonia (PCP) (18.5%), and multiple OI infections (10.4%). The mean duration of the ART-initiated treatment in all new cases was 97.4±324.7 days after HIV was diagnosed. Median of duration in rapid ART group was eight days compared with 36 days in the standard group ($p<0.001$). Based on the Thailand's National Guidelines on HIV/AIDS Treatment, 93.64% of the patients were treated with ART of non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen.

Males were predominant patients in both groups. The mean age of the patients in the ART group was 33.18±11.36 years and 34.50±11.21 years in the Standard group. Most of the patients were aged between 25 and 60 years. Most of the patients were heterosexual transmission. The median CD4 (IQR) levels at the initiation of the patients in the rapid ART group were 234 (102 to 345) cells/mm³ and 121 (37 to 282) cells/mm³ in the Standard group. The sexual transmission disease infection used the VDRL or TPHA assay for diagnosis, HBV coinfection and HCV coinfection between those two groups are demonstrated in Table 2. In the rapid ART group 73.28% were at an asymptomatic stage and only 46.58% in the Standard group. The OIs at the time of initiated ART between those two groups are demonstrated in Table 2. The most common OI was PCP with 27.59% in the rapid ART group and 16.78% in the standard group. Most of the patients did not perform the purified protein derivative (PPD) skin tests to the determination of latent tuberculosis infection. The primary ART regimen was NNRTIs with nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) based regimen with 93.39% in the rapid ART group and 93.79% in the standard group.

The primary outcome from the monitoring of the VL at 24 weeks, as shown in Table 3, was undetectable VL with 84.94% in the rapid ART group and 82.92% in the standard group. The secondary outcome of ART treatment at 72 weeks, overall found that 95.4% of the patients retained to care were virological suppression. The VL at 72 weeks, was undetectable with 97.14% in the rapid ART group and 93.84% in the standard group. There was no significant difference in the primary and secondary outcomes of undetectable VL in both groups at 24 and 72 weeks with p-values of 0.747 and 0.079, respectively. The unmasking immune reconstitution inflammatory syndrome (IRIS) was 2.48% in the

Table 1. Demographic data of newly diagnosed HIV patients

Characteristic	n=1,007
Age (year); mean±SD	34.03±11.27
Male; n (%)	710 (70.51)
Mode of transmission: heterosexual; n (%)	881 (87.49)
Hepatitis B coinfection; n (%)	125 (12.41)
Hepatitis C coinfection; n (%)	53 (5.29)
Sexual transmitted disease with syphilis; n (%)	75 (7.51)
HIV status: asymptomatic stage; n (%)	566 (56.21)
Opportunistic infection at ART initiate; n (%)	356 (35.35)
Tuberculosis	110 (30.90)
Talaromycosis	34 (9.55)
Cryptococcosis	22 (6.18)
Pneumocystis pneumonia	66 (18.54)
Multiple OI infection	37 (10.39)
Malignant related HIV disease	11 (3.09)
Cerebral toxoplasmosis	28 (7.87)
Salmonellosis	2 (0.56)
Sexual transmitted disease	35 (9.83)
Histoplasmosis	10 (2.81)
Unclassified opportunistic infection	1 (0.28)
CD4 level (cell/mm³); median (IQR)	268 (50 to 318)
ART based regimen with NNRTI; n (%)	943 (93.64)

ART=antiretroviral therapy; HIV=human immunodeficiency virus; OI=opportunistic infection; NNRTI=non-nucleoside reverse transcriptase inhibitors; SD=standard deviation; IQR=interquartile range

Table 2. Characteristics of newly diagnosed HIV patients classified by ART treatment group

	Rapid ART group (n=363)	Standard group (n=644)	p-value
Age (year); mean±SD	33.18±11.36	34.50±11.21	0.075
Day of initiation after diagnosis; median (IQR)	8 (6 to 12)	36 (23 to 68)	<0.001
Sex; n (%)			0.037
Male	241 (66.39)	469 (72.83)	
Female	122 (33.61)	175 (27.17)	
Age group; n (%)			0.248
15 to 25 years	110 (30.30)	164 (25.47)	
>25 to 60 years	246 (67.77)	469 (72.83)	
>60 years	7 (1.93)	11 (1.71)	
Transmission; n (%)			0.198
Heterosexual	311 (85.67)	570 (88.51)	
MSM	52 (14.33)	74 (11.49)	
CD4 level at initiation; n (%)			<0.001
<200	153 (42.27)	402 (62.71)	
201 to 350	124 (34.25)	139 (21.68)	
351 to 500	58 (16.02)	77 (12.01)	
>500	27 (7.46)	23 (3.59)	
Median (IQR)	234 (102 to 345)	121 (37 to 282)	<0.001
Sexual transmitted disease with syphilis; n (%)	30 (8.36)	45 (7.03)	0.674
Hepatitis B coinfection; n (%)	48 (13.26)	77 (11.99)	0.552
Hepatitis C coinfection; n (%)	13 (3.61)	40 (6.24)	0.079
HIV status: stage; n (%)			<0.001
Asymptomatic HIV	266 (73.28)	300 (46.58)	
Symptomatic HIV	38 (10.47)	44 (6.83)	
AIDS defining disease	59 (16.25)	300 (46.58)	
OI at/short after ART initiated; n (%)			<0.001
Tuberculosis	5 (8.62)	105 (35.23)	
Talaromycosis	5 (8.62)	29 (9.73)	
Cryptococcosis	3 (5.17)	19 (6.38)	
Pneumocystis pneumonia	16 (27.59)	50 (16.78)	
Multiple OI infection	4 (6.90)	33 (11.07)	
Malignant related HIV disease	4 (6.90)	7 (2.35)	
Cerebral toxoplasmosis	3 (5.17)	25 (8.39)	
Salmonellosis	1 (1.72)	1 (0.34)	
Histoplasmosis	1 (1.72)	9 (3.02)	
Unclassified opportunistic infection	0 (0.00)	1 (0.34)	
Purified protein derivation skin test; n (%)			0.339
Positive	4 (1.10)	4 (0.62)	
Negative	2 (0.55)	9 (1.40)	
Not done/missing data	357 (98.35)	631 (97.98)	
ART based regimen; n (%)			0.918
NRTIs/NNRTI based regimen	339 (93.39)	604 (93.79)	
NRTIs/PI based regimen	23 (6.34)	37 (5.75)	
NRTIs/INSTI based regimen	1 (0.28)	3 (0.47)	

ART=antiretroviral therapy; HIV=human immunodeficiency virus; OI=opportunistic infection; NRTIs=nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitors; PI=protease inhibitor; INSTI=integrase stand transfer inhibitors; SD=standard deviation; IQR=interquartile range

Table 3. The virological outcome after ART initiated treatment at 24 and 72 weeks

	Rapid ART group (n=363); n (%)	Standard group (n=644); n (%)	p-value
Virological response at 24 weeks			0.747
<40 IU/mL	282 (84.94)	466 (82.92)	
>40 IU/mL	34 (10.24)	64 (11.39)	
>200 IU/mL	16 (4.82)	32 (5.69)	
Virological response at 72 weeks			0.079
<40 IU/mL	306 (97.14)	503 (93.84)	
>40 IU/mL	5 (1.59)	14 (2.61)	
>200 IU/mL	4 (1.27)	19 (3.54)	
Occurring of unmasking IRIS	9 (2.48)	17 (2.64)	0.853
OI within 1 year after initiation of ART			0.730
Tuberculosis	11 (3.03)	11 (1.71)	
Talaromycosis	1 (0.28)	2 (0.31)	
Cryptococcosis	2 (0.55)	2 (0.31)	
Pneumocystis pneumonia	0 (0.00)	1 (0.16)	
Multiple OI infection	0 (0.00)	0 (0.00)	
Malignant related HIV disease	0 (0.00)	0 (0.00)	
Cerebral toxoplasmosis	0 (0.00)	1 (0.16)	
Salmonellosis	0 (0.00)	0 (0.00)	
Histoplasmosis	0 (0.00)	0 (0.00)	
Overall status			0.012
Alive	278 (76.58)	450 (69.88)	
Loss to follow up	19 (5.23)	43 (6.68)	
Refer out	49 (13.50)	86 (13.35)	
Mortality	17 (4.68)	65 (10.09)	0.003

ART=antiretroviral therapy; IRIS=immune reconstitution inflammatory syndrome; OI=opportunistic infection; HIV=human immunodeficiency virus

rapid ART group and 2.64% in the standard group with no clinically significant difference (p=0.853). The OI after ART initiation in one year was 3.8% in the rapid ART group and 2.63% in the standard group with no clinically significant difference (p=0.730). In rapid ART compared with standard ART, there were 4.68% and 10.09% dead with statistical significance (p=0.003). The LTFU rate in the rapid ART group was not statistically different from the standard group with 5.23% in rapid ART and 6.68 per in standard ART.

After adjusting for univariable analysis in Table 4, there was benefits of rapid ART treatment at first 24 weeks with risk ratio 0.491 (95% CI 0.25 to 0.95, p=0.035) compared to the standard treatment. However, after follow-up at 72 weeks, there was no clinically significant difference between rapid ART treatment and standard treatment with a risk ratio of 1.107 (95% CI 0.36 to 3.40, p=0.858).

After adjusting of age, gender, and mode of transmission, the CD4 level after at initiation, HIV co infection, and OI after ART treatment for virological outcome at 72 weeks are as shown in Table 5. The HCV coinfection, symptomatic/AIDS defining disease were associated with good virological outcome at 72 weeks with RR 2.85; 95% CI 1.44 to

Table 4. Effect of the virological outcome after ART initiated treatment at 24 and 72 weeks

Outcome	Risk ratio	Adjusted difference (95% CI)	p-value
Virological response at 24 weeks	0.491	0.71 (0.25 to 0.95)	0.035
Virological response at 72 weeks	1.107	0.02 (0.36 to 3.40)	0.858

CI=confidence interval

Table 5. Factor effect with good virological outcome at 72 weeks

Favorable factor	Risk ratio	95% CI	p-value
Male	1.19	0.68 to 2.06	0.537
Age less than 25 years old	1.60	0.84 to 3.05	0.151
MSM	1.52	0.85 to 2.73	0.159
Hepatitis C coinfection	2.85	1.44 to 5.61	0.003
Symptomatic/AIDS defining disease	1.85	1.13 to 3.01	0.012
Same day ART (1 to 7 days)	1.08	0.43 to 2.66	0.863
Rapid ART (1 to 14 days)	1.37	0.81 to 2.34	0.232

CI=confidence interval; ART=antiretroviral therapy

5.61, p=0.003 and with RR 1.85; 95% CI 1.13 to 3.01 p=0.012, respectively.

Discussion

Rapid ART treatment is suitable in the asymptomatic HIV stage and beneficiary for faster suppression of HIV VL, and avoidance of LTFU. However, patients who present with OI need to wait for two to six weeks after treatment of OI[20,21] to prevent IRIS or death, such as pulmonary TB should start ART after two weeks, patients with TB meningitis should start ART after four weeks, and patients with cryptococcal meningitis should start ART after four to six weeks after initial treatment.

The present study showed the result of the faster suppression of HIV VL at 24 weeks after rapid ART initiation with a clinically significant difference, but there was no clinically significant difference in virological suppression at 24 and 72 weeks in both rapid ART and standard treatment groups (p=0.747, 0.079, respectively). The rapid ART group had better retention of care than the standard group, but no clinically significant difference (p=0.012). HCV co-infection and symptomatic/AIDS defining diseases staging were a favorable factor associated with VL suppression at 72 weeks (p=0.003, 0.012, respectively).

One third of the patients in the present study presented with signs and symptoms of OI that caused the delay in ART initiation. ART was started two to six weeks later depending on the AIDS defining illness. Therefore, the standard group had a higher mortality rate with a clinically significant difference related to their illness.

The primary cause of death of those patients who received ART was unknown in 2.45%, malignancy in 1.57%, or bacteremia such as sepsis, pneumonia in 1.08%. The LTFU rate between those two groups was not associated with mortality. Only MSM and age less than 25-years-old were unfavorable factor of death in the present study with statistical significance (RR 6.93, 95% CI 1.65 to 29.01, p=0.008; RR 2.13, 95% CI 1.27 to 3.58, p=0.002, respectively).

A study in 70 newly diagnosed HIV infections with high CD4 in the U.S.[12] also found rapid start of ART within seven days archived viral suppression earlier than non-rapid start of ART with statistical significance (p=0.03) but these studies did not show long term clinical outcome. In the rapid initiation of ART within 24 hours after diagnosis of HIV infection in the U.S. population, 94.9% of rapid ART had a significantly faster virological suppression compared to universal ART with a median time of viral suppression of 1.8 and 4.3 months, respectively (p<0.001), with 10.3% LTFU[8]. Early ART initiation promises earlier virological suppression[8,12,22,23].

The strength of the present study is that this study was conducted with a large scale of newly diagnosed HIV patients with close follow-up of at least 72 weeks. The limitation of the present study is the use of a single center-based information, which does not represent a generalization of the population of the country. The patients in the rapid ART treatment group had better availability to care than the standard treatment group, resulting in better outcomes. Further study will require determination in multiple sites of the information for generalization of the varied population.

The success of long-term VL suppression was the retention of care. The process of retention to care consists of a good patient-doctor relationship, mental health support, and solving psychosocial problems for sustained VL suppression[24]. Chosen medication with less pill burden regimen, various options of suitable regimen, good counseling of drug compliance, and side effects improve retention of care. Thailand's National AIDS Program provide a combination regimen of HAART for decreased pill burden, which is one of the important issues for achieving good adherence and VL suppression[25,26]. Consistent with the study from Ethiopia[27], using a single-tablet regimen of dolutegravir-based regimen had improved VL suppression from 81.4% to 92% compared with a non-single tablet regimen. The loss of follow-up of the patients was another important factor related to VL non-suppression and poor long-term outcomes as studied in Johannesburg[28]. So, the key to success of long-term HAART treatment is tracking of LTFU, which is a mainstay to achieve VL suppression overall.

Conclusion

There was higher rate of virological suppression at 24 weeks in rapid ART group. However, there was not significantly difference in virological suppression in both groups at 72 weeks. There was better retention to care and lower mortality rate in the rapid ART group. LTFU rate was not different between the groups.

What is already known on this topic?

Same day ART showed faster virological suppression in newly HIV cases. Rapid ART or standard care in this hospital showed no difference in

long-term virological outcome in PLWH who retained to care and were not lost to follow up. Benefit in lower mortality was found in rapid ART group.

What this study adds?

PLWH who follow-up the care will achieve long-term virological outcome. Tracking of LTFU is a mainstay to achieve the good outcome.

Acknowledgement

The authors would like to thank all staffs working at the adult HIV clinic and Chiangrai Prachnukroh Hospital for their support.

Conflicts of interest

All authors declared no competing interests.

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