

Association Between Antiretroviral Therapy Adherence and Clinical Outcomes among Human Immunodeficiency Virus Patients at Medication Therapy Adherence Clinic

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Abstract

Human Immunodeficiency virus (HIV) negatively impacts the immune system, particularly CD4 count, and causes acquired immune deficiency syndrome (AIDS)-related illnesses and death. Most HIV patients have a decrease in viral load (VL) at the start of antiretroviral therapy (ART), but recovery of CD4 count varies. The objective of the study is to determine the association between clinical outcomes among HIV patients and antiretroviral therapy adherence. A retrospective cross-sectional study was conducted at the infectious disease (ID) clinic. HIV patients started on antiretroviral therapy (ART) were recruited and followed up for a minimum of 6 months with at least one Malaysia Medication Adherence Assessment Tool (MyMAAT) done by pharmacist at Retroviral Disease Medication Therapy Adherence Clinic (RVD MTAC). Data were retrieved using a data collection form and analyzed using SPSS version 25. A total of 30 subjects were recruited with 93.3% of patients were categorized as good adherence (score ≥ 54) based on MyMAAT. The median self-reported adherence score was 60 [IQR: 59-60]. The median pharmacy refill adherence rate was 100% [IQR: 99.9-100]. Using pharmacy refill adherence rate, patients were categorise using threshold of $> 90\%$, 93.3%

were adherent to ART. An exploratory analysis showed that, there were significant difference between the CD4 count pre and post ART among those with good adherence. There was significant difference between clinical outcome (baseline CD4 and CD4 post antiretroviral initiation) among HIV patients who were having good adherence towards antiretroviral therapy.

Keywords: Antiretroviral therapy, human immunodeficiency virus, pharmacy refill, CD4 count, medication therapy adherence clinic.

Introduction

The HIV negatively impacts the immune system, particularly CD4, and spreads through the interchange of various bodily fluids from an infected individual, including vaginal secretion, rectal fluid and breastmilk. (1). The viral load (VL) can be transmitted to another person that can cause the risk of HIV infection (2). Most persons have a drop in plasma viral load (VL) following the start of antiretroviral (ARV) medication to an undetectable level within three months. However, recovery of CD4 count in people on ART varies. ART has shown remarkable success in controlling HIV replication and significantly reducing morbidity and mortality, but it cannot cure HIV and

requires lifelong medication (3). Hence, maintaining long-term adherence to antiretroviral therapy (ART) is required for attaining the intended treatment outcome, which is HIV suppression at an undetectable level. Poor ART adherence is associated with threatening the patients' health, ineffective viral suppression and likelihood of long-term treatment aversion to the ARV medication. (4). According to a meta-analysis involving 43 studies, there are only 63.4% patients ($n = 17,746$) from 26 countries on average reported having optimal adherence (5). According to Bezabhe et al. (2016), the correlation between virologic and adherence differed depending on the adherence assessment tools. The meta-analysis undermines the reliability of using self-reported adherence as a marker for virologic outcomes. A significant number of patients who reported high adherence experienced virologic failure. Self-reported adherence is susceptible to biases, such as social interest and recall bias, which patients may overstate their actual adherence levels. "The Malaysia Medication Adherence Assessment Tool (MyMAAT) is a professed adherence assessment tool to determine ART adherence of HIV patients during their visit at Retroviral Disease Medication Therapy Adherence Clinic (RVD MTAC) (6). Pharmacy refill adherence was the second-most common assessment tool, followed by pill counts, electronic medical device use and plasma drug concentration (7). RVD MTAC is one of the MTAC conducted by trained pharmacists in collaboration with infectious disease specialist and dedicated nurses in government hospitals. On the first RVD MTAC visit, pharmacists will conduct counselling for the patients by referring to the HAART initiation counselling checklist. For the subsequent visits, pharmacists will review patients' adherence to medication by using MyMAAT, review patient's tolerability, drug toxicities and reinforce the effectiveness of adherence to ART (8). Majority of HIV patients self-reported that they were adherent to the ART during RVD MTAC visit. Upon review of

PhIS, it was noted that some of the patients did not adhere to pharmacy refill date given. To date, there is no local study on pharmacy refill adherence among HIV patients on ART. Moreover, there is also no local study on the association between ART adherence and clinical findings. The study will help pharmacists to improve on ART adherence assessment, detecting non-adherence among HIV patients and hence improves patients' clinical outcomes. The study aims to identify the association between adherence to ART through self-reported, pharmacy refill assessment tools and clinical outcomes between HIV patients.

Materials and Methods

Study setting and design

This study was a retrospective, non-interventional and cross-sectional study done at tertiary hospital, Hospital Raja Permaisuri Bainun (HRPB), Ipoh, Perak, Malaysia using universal (consecutive) sampling. The study duration was between June 2021 until February 2022. The information on basic demography, retroviral disease history, self-reported adherence, pharmacy refill adherence as well as the clinical outcomes of the patients were collected using data collection form, from Hospital Information System (HIS) and Pharmacy Information System (PhIS).

Study Subjects

At the onset of this study, patients are assessed for eligibility base on inclusion and exclusion criteria. HIV patients ≥ 18 years old, started ART at ID Clinic and counselling done by pharmacist at RVD MTAC and attended ID Clinic, HRPB Ipoh between June 2021 until February 2022 for a minimum of 6 months follow up with at least one MyMAAT done by pharmacist at RVD MTAC were recruited in this study. Patient with incomplete medical records or was given manual prescription or were collecting part supply medication at other hospital (SPUB) or those without VL or CD4 count 6 months post ART were excluded.

Malaysia Medication Adherence Assessment Tool (MyMAAT) was utilized to measure patients' self-reported adherence during RVD MTAC visit. The self-reported ART adherence result was documented inside the RVD MTAC counselling records (PhIS) by the attending pharmacist. In this study, MyMAAT before CD4 count result at 6 months post ART were collected. MyMAAT composed of 12 questions, with maximum score of 60 and minimum score of 12. The Patient's adherence were identified based on the total score : Good adherence = total score of ≥ 54 ; Moderate and poor adherence = total score of < 54 .

Data on pharmacy refill ART adherence (date and quantity of medications dispensed) was collected from the PhIS or Value-added Service (VAS) excel database. Pharmacy refill adherence rate per HIV patient was calculated using the formula by Gaifer and Boulassel, 2019.

$$= [(Amount\ of\ pills\ dispensed / Amount\ of\ pills\ per\ day) / days\ between\ refills] \times 100\%$$

Adherence to refills was deemed 100% if all pills were provided on time during the designated refill window. Refill adherence values above 100% for patients who refilled before the scheduled date were rounded down to 100%." (10). Previous study by Gaifer and Boulassel, (2019), categorised the patients into adherent group if the adherent rate is $>90\%$. Clinical outcomes in the study were measured as viral load and CD4 count 6 months post antiretroviral therapy as recommended by WHO, 2013.

Statistical Analysis

SPSS program version 25.0 was used to conduct the statistical analysis. Normality of numerical data was checked using skewness and kurtosis. Continuous data that followed a normal distribution were summarized using descriptive statistics such as the mean and standard deviation (SD), while non-normally distributed data were summarized using the median and interquartile range (IQR). Categorical data were presented as frequencies, percentages, and 95%

confidence interval (CI) where applicable. Continual variables were measured using comparative statistics of Wilcoxon Signed Rank test. Pearson Correlation was used to ascertain the correlation between ART adherence and clinical outcomes. Statistical significance will be assigned to a P-value of less than 0.05. Results were presented in tabulation and graphical illustrations were added to explore the trending of the cases. Missing data was not replaced.

This study was enlisted under National Medical Research Register (NMRR ID-22-01219-GZ9) and was approved by Medical Research and Ethics Committee (MREC). Informed consent waiver was applied through MREC as it was not feasible to obtain informed consent personally from HIV patients to use their data for this study as it was done prospectively. Patient data was kept strictly confidential, whether in hardcopy or digital form. Additionally, all information collected will be securely stored in locked facilities for two years for analysis and publication purposes, after which it will be permanently discarded. Personal identities will not be disclosed, and subjects will not be identifiable in the study's findings.

Results and Discussion

Demographic Characteristics of Study Patients

Table 1 showed a demographic characteristic of 30 patients enrolled in the

Table 1: Demographic characteristics of the Study Population

Characteristics	Value
Gender	
Males, n (%)	27 (90.0)
Females, n (%)	3 (10.0)
Age, years	
Median [IQR]	32.5 [25.0-39.3]
Mean (SD)	32.5 (8.3)
Min	20
Max	53
Ethnicity	
Malay, n (%)	19 (63.3)
Chinese, n (%)	6 (20.0)
Indian, n (%)	5 (16.7)

study. Majority 90% (n=27) of the patients were male with only 10% (n=3) female. The age range was from 20 to 53 years old with mean (SD) of 32.5 (8.3) years. In terms of ethnicity, majority 63.3% (n=19) of the patients were Malays, followed by Chinese, 20% (n=6) and Indians, 16.7% (n=5).

This study is similar to the previous study that reported the majority of the study participants in an ART adherent study done in Malaysia were males 76.3% (n=706) (9). In 2019, 69% of newly diagnosed HIV were homosexual men (MSM) (10). Most of the patients were in the age range between 20-39 (77%) (10). This study showed that the enrolled study participants were mainly Malays followed by Chinese and Indians. According to Abiola et al. (2015), Malays made up the majority of study participants (48.3%), followed by Chinese (40.5%), Indian (9.1%) and others (2.1%). The disparity could be attributed to Malaysia's overall proportion of the three ethnicities (11).

Antiretroviral Therapy Adherence among the Study Population

The ART adherence among the study population is as shown in (Table 2). The median self-reported adherence score was 60

Table 2: Demographic characteristics of the Study Population	
Type of Adherence Assessment	Value
Self-reported Adherence Score, value	
Median [IQR]	60 [59-60]
Mean (SD)	59.1 (2.0)
Good Adherence (Score \geq 54), n (%)	28 (93.3)
Moderate and poor adherence (Score <54), n (%)	2 (6.7)
Pharmacy Refill Adherence Rate, percentage (%)	
Median [IQR]	100 [99.9-100]
Mean (SD)	98.3 (4.4)
Adherent (Adherence Rate \geq 90%), n (%)	28 (93.3)
Nonadherent (Adherence Rate < 90%), n (%)	2 (6.7)

[IQR: 59-60]. Majority 93.3% (n=28) patients were categorised as good adherence (score \geq 54) based on MyMAAT, only 6.7% (n=2) patients were categorised as moderate to poor adherence (score < 54). The median pharmacy refill adherence rate was 100% [IQR: 99.9-100]. Using pharmacy refill adherence rate threshold of > 90%, 93.3% (n=28) patients were classified as adherent and 6.7% (n=2) patients as nonadherent.

Majority of patients were categorized as good adherence, and it was possible due to role of pharmacist in the RVD MTAC. This is supported by the evidence that engagement of pharmacists in the management to the patients with positive HIV can improve patient outcomes such as increase adherence, higher in CD4 count and increase amount of viral suppression (12). A systematic review and meta-analysis by Ahmed et al. (2021) found that PLHIV can be improved by pharmacist care which can enhance the adherence, VL suppression, and CD4 count. (13).

Using pharmacy refill adherence rate threshold of > 90%, most of the patients were classified as adherent. This might be due to the Value-added Services such as mail delivery or Ubat Melalui Pos (UMP) provided by pharmacy HRPB Ipoh, increased the convenience of the patients in getting their monthly ART supply. This is supported by Cruz et al. (2018), some techniques that enhance drug availability, such as ARV mail delivery, may improve the adherence.

Clinical Parameter and Clinical Outcomes of the Study Population

Table 3 showed that the median baseline CD4 counts were 54 [27.5-171.5] cells/mm³. Meanwhile, median CD4 count post ART were 232 [143-325] cells/mm³. The study findings revealed that the median increased in CD4 count were 150 [130-224.8] cells/mm³. The median viral load post ART were 19 [19- 29.8] copies/ml. Almost 73.3% (n=22) patients achieved viral load suppression (VL < 20 copies/ml or not detectable), only 24.5% (n=8) patients did not achieve viral load suppression post ART.

In subgroup analysis, Wilcoxon signed rank test revealed that the median of CD4 count post ART (Median = 221.50) was significantly higher than the median CD4 count pre ART (Median = 54) in the self-reported adherence group, $z = -4.577$, $p = 0.000$ (Table 4). The median of CD4 count post ART (Median = 232) was significantly higher than the median of CD4 count pre ART (Median = 68.5) in the pharmacy refill adherence group, $z = -4.577$, $p = 0.000$ (Table 4).

Our study results showed that median of a CD4 count (54 cell/mm³) was higher

Table 3: Clinical Outcomes Pre and Post ART among the Study Population

Clinical Parameters	Value
CD4 counts, cells/mm ³	
Pre ART	
Median [IQR]	54 [27.5-171.5]
Mean (SD)	128.6 (160.4)
Post ART	
Median [IQR]	232 [143-325]
Mean (SD)	285.8 (214.7)
Increased in CD4 counts, cells/mm ³	
Median [IQR]	150 [103-224.8]
Mean (SD)	174.7 (103.8)
Viral Load Post ART, copies/ml	
Median [IQR]	19 [19-29.8]
Mean (SD)	30.4 (24.5)
Viral Load Suppressed, VL < 20 copies/ml or ND	
Yes, n (%)	22 (73.3)
No, n (%)	8 (26.7)

compared to other study with median baseline of 257cells/mm³ (Asfaw et al., 2015). The rate and amount of CD4 counts recovery vary greatly among PLHIV with various baseline CD4 count (14). In Nepal, a cross-sectional study was performed and found that the mean CD47 count of patients taking ART after six months was as high as 501 cells/mm³ (15).

Baseline VL was not done in patients treated at ID clinic, HRPB Ipoh due to unavailability of the test in the setting and the results took 2 weeks to come back if outsource the test. Most of the HIV patients seen at ID clinic, HRPB Ipoh would have started on ART once the HIV diagnosis was confirmed. Optimal viral suppression is defined as a VL that is consistently below the detection level (VL < 20 to 75 copies/mL, depending on the test used) (16). A total of 49.2% of patients was noticeable absent of virus in the plasma, while 42.2% develop virological failure (viral load, ≥1000 copies/mL) according to WHO criteria (16).

CD4 counts were significantly higher after starting the ART as compared to before in both self-reported and pharmacy refill adherent patients. Research from ID clinic in New Mexico found that a pharmacist-led MTAC providing ARV adherence counselling not only boosted adherence but also improved CD4 count and viral load (17,18). The association between adherence and CD4 count is proven by Tchakoute et al. (2022), who showed that a 10% rise in adherence was linked to 8.54 cells/mm³ increase in mean CD4 count over six months (p-value <0.0001).

Table 4: CD4 count Pre and Post Antiretroviral Therapy Among the Adherent Study Population

Variables	Good Adherence (Self-reported) (N=28)		Z statistic ^a	P- Value ^a
	Pre ART	Post ART		
	Median [IQR]	Median [IQR]		
CD4 count, cell/mm ³	54 [28.25-176.50]	221.50 [141.00-343.00]	-4.557	.000**
Variables	Adherent (Pharmacy Refill) (N=28)		Z statistic ^a	P- Value ^a
	Pre ART	Post ART		
	Median [IQR]	Median [IQR]		
CD4 count, cell/mm ³	68.5 [28.25-176.50]	232.00 [144.75-343.00]	-4.577	.000**

^aWilcoxon Signed Rank

*P-value <0.001 shows statistical significance

Antiretroviral Therapy Adherence and Clinical Outcomes

Table 5: Association Between Adherence Results and Patients' Clinical Outcomes		
Association	Pearson correlation coefficient ^a	p value ^a
Self-reported adherence score vs.		
Increased in CD4+ T cells count post ART	0.042	0.828
Viral load post ART	0.182	0.345
Pharmacy refill adherence rate vs.		
Increased in CD4 + T cell count post ART	0.092	0.630
Viral load post ART	0.173	0.360
^a Pearson Correlation		

Association Between ART Adherence and Patients' Clinical Outcomes

Table 5 showed that there was no correlation between the self-reported adherence score over increased in CD4 count post ART, [$r(28) = 0.048$, $p = .828$]. The correlation between self-reported adherence score over viral load post ART was not significant [$r(28) = 0.182$, $p = .345$]. This study also found that there was no correlation between pharmacy refill adherence rate over CD4 count post ART [$r(28) = 0.092$, $p = .630$]. The correlation between pharmacy refill adherence rate over viral load post ART was not significant, [$r(28) = 0.173$, $p = .360$].

This study showed that there was no correlation between ART adherence and clinical outcomes either through self-reported or pharmacy refill adherence assessment. Tchakoute et al. (2022) revealed that adherence levels were significantly associated with CD4 count, as shown by a regression coefficient of 8.54 for a 10% increase in adherence (p -value <0.0001). A marked reduction in viral load was also highly correlated with sustained adherence, with a regression coefficient of -0.06 for a 10% rise in adherence (p -value <0.0001). Higher adherence was associated with a reduction in viral load but no significant correlation between change in CD 47 count with adherence. (19,20). However, the reason was not mentioned in the study findings.

There are advantages and disadvantages of assessing ART adherence by using different types of assessment tool. Pharmacy refill assessment tool is unsuitable if patients request to collect part supply medication at other hospital through SPUB service. Moreover, adherent to pharmacy refill

do not align with the prescribe dosing regimen (21,22,23). Self-reported adherence assessment tool has been shown to overstate adherence by 10% to 20% (11,24). However, it is the best tool to explore reason for nonadherence (8,25,26).

Research Limitations

As with all studies, there were some limitations to this study. This study has a relatively small sample size compared to previous study. In previous studies by Gaifer and Boulassel. (2019), the number of subjects were 153 patients whereas in this study it was only 30 patients. The small sample size was due to the short duration of study period. MyMAAT was only incorporated in pHIS MTAC module starting from 25th May 2021, and relatively small number of subjects can be enrolled each month after being filtered by inclusion and exclusion criteria. Besides, variables for clinical outcomes such as CD4 and VL 6 months post ART need to be collected. Our finding has limited statistical power due to small sample size.

The study was a retrospective review using routinely available data documented, such as MyMAAT, amount and duration of ART supplied in pHIS. The accuracy of the data may have influenced the outcomes of the study. Self-reported adherence data raised the possibility of reporting bias, recalling bias, and the tendency for respondents to overestimate drug adherence. Although pharmacy refill adherence assessment tool might be a good tool for assessing ART adherence, but to work out a PLHIV take medication from pharmacy was difficult to ascertain that a PLHIV took their medication after collecting it from the pharmacy.

A potential limitation of this study was lack of baseline viral load. The failure rates were determined based on a single point testing of CD4 count and VL after six months of ART. The impact of other factors such as comorbidities, number of medications, duration of disease, patients' understanding/knowledge of ART and HIV on adherence, VL and CD4 counts were not considered in the study. Therefore, unmeasured confounding factor cannot be eliminated.

Conclusion

In conclusion, this study showed that majority of the HIV patients treated at Infective Disease Outpatient Clinic Hospital Raja Permaisuri Bainun Ipoh had good ART adherence in both self-reported and pharmacy refill adherence assessment. This study showed that there was an impact of MTAC pharmacist counselling that not only boosted adherence but also improved CD4 count of patients. However, the study was unable to prove that either self-reported or pharmacy refill ART adherence assessment tool was better to predict clinical outcomes among HIV patients. The findings from the study help pharmacists to improve on ART adherence assessment among HIV patients. Besides, it helps to improvise pharmacists' role in detecting HIV patients that non-adhere to ART and non-improving clinical outcomes.

Future multi-centers prospective study with extensive duration and larger sample size is proposed to obtain a statistically significant finding on the association between antiretroviral therapy adherence and clinical outcomes in local setting. This study can be further expanded in the future to look into other aspects of outcomes including opportunistic infection, hospitalization and quality of life.

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