A Randomised Pilot Study on the Impact of Pharmacists' Telephone Follow-Up on Medication Adherence among Patients Receiving Antiretroviral Medication Delivered Through Postal Service (MDPS)

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ABSTRACT

Introduction:

Adherence to antiretroviral therapy (ART) remains a great challenge. Close monitoring is required at all times to rapidly identify non-adherent patients, establish the causes, and find suitable solutions. This pilot study investigated the impact of pharmacists' telephone follow-up — Enhanced Pharmacist-Assisted Service in Antiretroviral Therapy (EPAS-ART), on top of the standard care on ART adherence among patients receiving ART via Medication Delivered through Postal Service (MDPS).

Methods:

Patients who receive ART medication from Hospital Pulau Pinang were randomly assigned to either EPAS-ART in addition to the standard care, or the standard care alone. The EPAS-ART intervention offers monthly telephone follow-up sessions over six months to review patients' medication adherence, adverse drug reactions, and medication concerns, followed by individualised recommendations to address any identified issues. The primary outcome was self-reported medication adherence by pill counting at 6 months.

Results:

A total of 60 patients on ART medication with a mean age of 41.28 ± 10.17 years, completed the 6-month follow-up. The age, gender, ethnicity, ART regime, and duration of ART were similar between the EPAS-ART group and standard care group. There was slight improvement from baseline to 6 months follow-up in self-reported medication adherence for the EPAS-ART group, and a slight decline in the standard care group. However, there were no significant differences between the groups in mean self-reported medication adherence (P=0.062).

Conclusion:

The study showed no statistically significant difference in self-reported medication adherence between the EPAS-ART and standard care groups. However, the intervention had an impact on maintaining optimum medication adherence among patients in the EPAS-ART group with an early detection of patients' adverse drug reactions to the ART regimen.

Keywords:

Telephone, follow-up, medication adherence, antiretroviral medication, postal service

INTRODUCTION

Globally, there are currently an estimated 38 million people living with human immunodeficiency virus (HIV), mostly in middle- and low-income countries.[1.] Antiretroviral therapy (ART) provides promising outcomes in restoring immune function and reducing HIV-related morbidity and mortality.[2.] It has transformed acquired immune deficiency syndrome (AIDS) from an inevitably fatal disease into a chronic, manageable illness. However, the benefits of ART are limited by poor adherence, which often leads to treatment failure, more resistant viral strains, and progression to AIDS, as well as higher mortality rates, higher hospitalisation rates, and longer stays in hospital.[3] Poor medication adherence also has public health implications, as the transmission of resistant strains leaves the newly infected with limited therapeutic options. A 2011 meta-analysis, which pooled the ART adherence of 33,199 adults in 84 observational studies, reported that only 62% of individuals took at least 90% of their prescribed ART doses.[4] Studies on ART adherence reported healthcare facility determinants of non-adherence to ART, including long waiting times and limited operating hours to get the medication.[5,6] A feasible and acceptable set of interventions to enhance ART adherence is urgently needed to ensure the continued success of the clinical and financial sustainability of the global ART scale-up.

The use of mail to deliver medication to patients' homes has been shown to not only provide better access to medication efficiently and cost-effectively, but has also been reported to improve medication adherence.[7] During the COVID-19 pandemic, many countries adapted home medication delivery services to support the continuation of ART. An article gathering experience from four countries, including Indonesia, Laos, Nepal, and Nigeria, mentioned that home delivery of ART medications is a promising option to ensure safe and sustained access to uninterrupted lifesaving treatment among people living with HIV where COVID-19-related lockdowns and quarantines were imposed.[8] In most of the public healthcare facilities in Malaysia, the home medication delivery service, known as Medicine Delivered through Postal Service (MDPS), was introduced two decades ago as part of an effort to extend pharmacy services and mitigate the long wait times at pharmacy outpatient counters. In this service, patients' follow-up medicine, including ART, is delivered via mail to their home, office, or the

destination they choose monthly until their next clinic appointment. A recent review of the MDPS as part of pharmacy value-added services offered in Malaysia reported a high level of satisfaction among the service users.[9] However, as reported elsewhere, the primary concern was the lack of access to healthcare providers for information provision or counselling when medications were refilled via mail delivery. [10]

Therefore, in the absence of direct healthcare provider involvement in home drug delivery services, mobile phones serve as an important adjunct to meet patients' educational and informational needs. In an updated systematic review evaluating the effectiveness of mobile phone interventions, two-way communication was shown to improve ART adherence, with one trial involving phone calls demonstrating a reduction in viral load.[11] In line with this, a few previous studies reported that participants preferred the intervention through their mobile phone not only to act as a reminder but also as a useful source of information on HIV/AIDS, as well as allowing them to enquire about their illness or simply to communicate with their providers.[12,13] Despite the encouraging findings, so far, there was only one study conducted in Malaysia on the effectiveness of mobile phone reminders and peer counselling on ART adherence, viral load, and CD4 counts.[14] To date, no data are available on the mobile phone intervention among RVD patients using MDPS.

The objective of this study was to investigate the impact of Enhanced Pharmacist-Assisted Service in Antiretroviral Therapy (EPAS-ART) in addition to the standard care on ART adherence among patients receiving ART via MDPS. This study also aimed to determine the adverse drug reactions (ADR) associated with ART in the study population.

METHODS

Participants

Participants were recruited from the Infectious Disease Clinic in Hospital Pulau Pinang, Malaysia, from November 2021 to June 2022. The participants included were (i) adults aged 18 years and older with a new prescription of ART for at least six months, (ii) on ART for at least one month before enrolment, and (iii) opted to receive ART via MDPS. Patients who planned to transfer to another facility at the point of recruitment or who did not have access to mobile phones that could be contacted were excluded.

Sample Size Calculation

Prior findings indicated that the mean (SD) of ART adherence in the intervention group receiving telephone follow-up was 95.7% (1.6%) and the control group was 87.5% (9.9%).[14] By taking an expected difference of 8.2 with a conventional level of significance of 5% and a study power of 90%, the minimum sample size was 23.[15] Thus, the required sample size was 29 after taking into account a 20% loss of follow-up. Subsequently, the number was rounded to 30 patients per group.

Recruitment Procedure

All the RVD patients on ART received standard care which consisted of infectious disease physician consultation during their follow-up day and extensive medication counselling by pharmacists. Patients were advised to contact the pharmacy in the events of experiencing any ADR or if they needed additional information. Patients have no direct contact with the healthcare providers until their next appointment.

Eligible patients were approached and their written consents were obtained. The patients were briefed on the study protocal and the possibility of receiving calls from pharmacists. Participants' demographic data, including contact details, clinical information, and current ART medications, were collected during baseline assessment upon randomisation at the clinic.

Randomisation and Blinding Procedures

This was an open-label study, where participants were randomly assigned to the EPAS-ART group or standard care group using blocked randomisation with a block size of four. The computer-based randomisation sequence was generated using a randomisation software [http://www.randomization.com]. The randomisaion was conducted by a project assistant who was not involved in participants' recruitment and follow-up. The randomisation sequence was concealed in consecutively numbered opaque envelopes. Once the eligible patients had consented to participate the study, the investigator opened the concealed envelope and assigned the participants randomly.

Intervention

EPAS-ART provided additional monthly telephone follow-up sessions alongside standard care over a six-month period. The intervention was delivered by two trained and experienced pharmacists, each with at least five years of experience in medication management among RVD patients. An initial call was attempted during the first week to inform participants about the scheduled follow-up calls at the fourth week. Participants were also provided with the clinic contact number to allow rescheduling in the event of other commitments.

For participants who missed the scheduled call, two call attempts were made on the same day, followed by one attempt per day over the subsequent two days. Those who did not return the follow-up call after these attempts were considered lost to follow-up and were dropped from the study.

The pharmacists followed a standard template adapted from the Retroviral Disease Medication Therapy Adherence Clinic (RVDMTAC) module of the Ministry of Health Malaysia to guide their conversation with the participants. The self-reported medication adherence, medication concerns, ADR, reasons for missed dose and any recent hospitalisation or emergency care visits were reviewed during the call. The phone call length

varied by needs of the participants and clinical judgement of the pharmacists. Most calls averaged at about 10–15 minutes. All the data gathered by the pharmacists during the calls were documented.

Outcome Measures

Participants in both the intervention and standard care groups were contacted at 1 month to assess baseline self-reported medication adherence. At 6 months, self-reported ART adherence was evaluated during follow-up at the RVDMTAC.

Self-reported medication adherence was measured by self-reported fill, which was determined by the number of pills that should have been taken over one month minus the number of pills taken during that month, divided by the total number of pills that should have been taken, and expressed as a percentage. In short, the medication adherence was calculated as such:

$$\text{Self-reported medication adherence} = \frac{\text{Number of pills dispensed - Number of missed dose}}{\text{Number of pills to be taken}}$$

Statistical Analysis

Descriptive statistics and inferential statistics were used to compare baseline characteristics and medication adherence among intervention and control groups. Pearson's Chi-square test was used for categorical variables, and independent t-test was performed for continuous data. In EPAS-ART, the patient reported ADR, and the reasons for missed doses were documented and analysed descriptively. Statistical significance was defined as $P \leq 0.05$. All statistical analyses were conducted using IBM SPSS Statistics 25.

RESULTS

The overall mean age of 60 respondents was 41.28±10.17 years and ranged from 24 to 67 years. The majority were male (68.3%) and of Malay ethnicity (51.7%). The mean number of years of patients on ART was 4.53±2.17 years. Disposition of study participants is shown in Figure 1. At baseline, there were no significant differences in age, gender, ethnicity, ART regimen or duration on ART between the intervention and standard care group at baseline (Table 1).

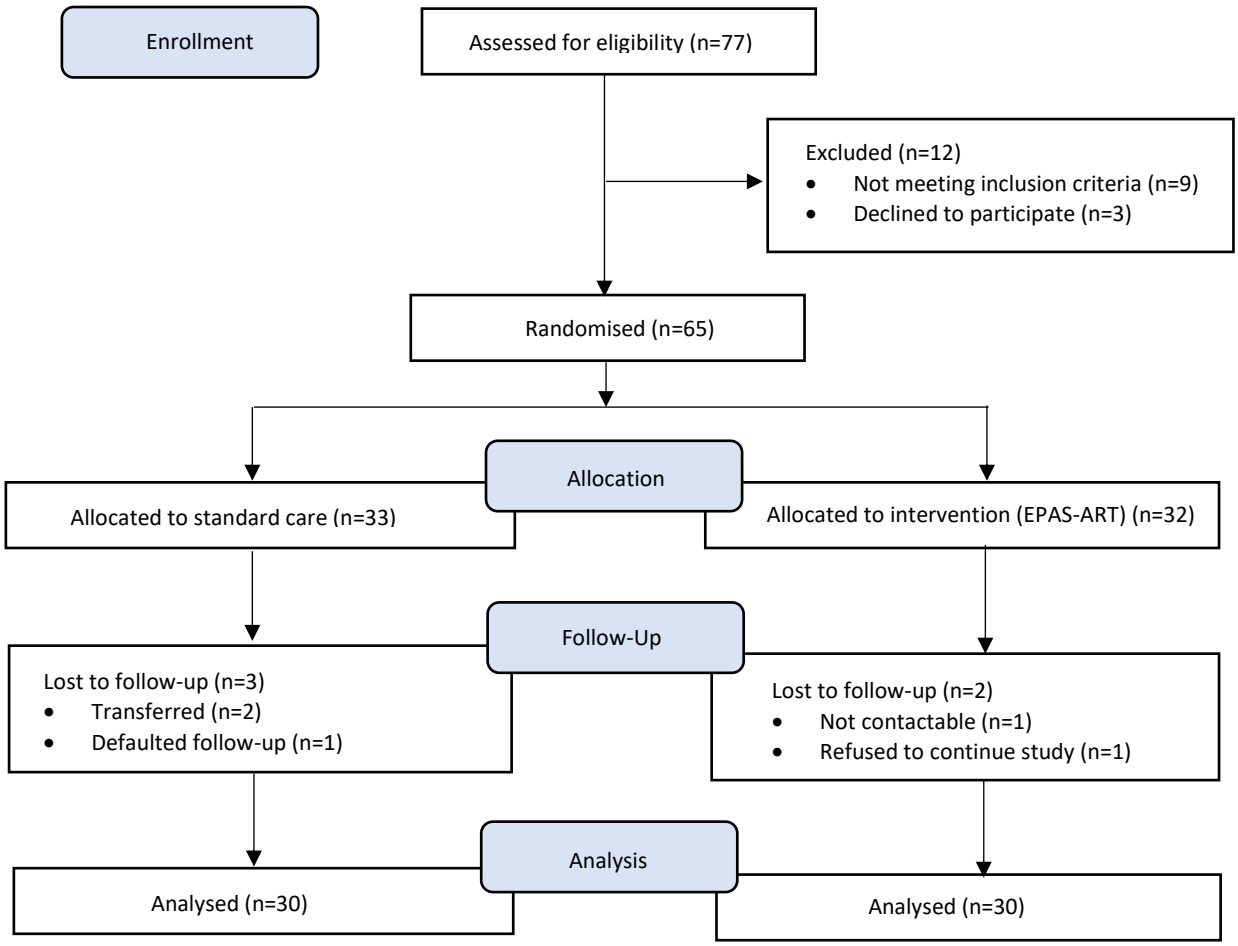

Figure 1. CONSORT flow diagram

Table 1. Baseline characteristics of participants (n=60)

Characteristics	n (%)			*P*-value
	Overall (n=60)	EPAS-ART + Standard care (n=30)	Standard care (n=30)	
Age in years; mean±SD	41.28±10.17	43.53±12.08	39.03±7.34	0.086[a]
Gender				
Male	41 (68.3)	20 (66.7)	21 (70.0)	0.500[b]
Female	19 (31.7)	10 (33.3)	9 (30.0)	
Ethnicity				
Malay	31 (51.7)	16(53.3)	15 (50.0)	0.809[b]
Chinese	17 (28.3)	9(30.0)	8 (26.7)	
Indian	12 (20.0)	5(16.7)	7 (23.3)	
Duration on ART in years; mean±SD	4.53±2.17	4.89±2.47	4.20±1.81	0.064[a]
ART regime				
Tenofovir + Emtricitabine + Efavirenz	35 (58.3)	19 (63.3)	16 (53.3)	0.432[b]
Others	25 (41.7)	11 (36.7)	14 (46.7)	

ART= Antiretroviral therapy; SD=standard deviation; EPAS-ART= Enhanced Pharmacist assisted service in antiretroviral therapy
[a]Independent t-test; [b]Pearson's Chi-square test

Table 2 highlights the differences in the self-reported medication adherence at baseline and after 6 months between the EPAS-ART and standard care groups. There was improvement from baseline to 6 months follow-up in self-reported medication adherence for the EPAS-ART group, and a slight decline in the standard care group. However, the mean change in medication adherence between the groups was not statistically significant.

Six (20.0%) ADR were reported during the first phone follow-up at 1 month in the EPAS-ART group. The reported ADR included diarrhoea, lipodystrophy, dizziness, insomnia, and vivid dreams (Table 3). The total number of ADR reported was reduced to four cases at 6 months. The reasons for missed doses reported during the follow-up include forgetting (n=6) or being busy (n=5).

Table 2. Self-reported medication adherence in EPAS-ART and standard care groups at baseline and at six months (n=60)

Groups	Self-reported Medication Adherence, % (mean±SD)		Change in Self-reported Medication Adherence, % (mean±SD)	Mean Difference (95% CI)	*P*-value[a]
	Baseline	6- month			
EPAS-ART (n=30)	99.83±0.67	99.96 ±0.21	0.13 ± 0.61	0.57 (-0.03,1.17)	0.062
Standard care (n=30)	99.50±1.17	99.06±1.73	-0.44 ± 1.52		

SD=standard deviation; EPAS-ART=Enhanced Pharmacist assisted service in antiretroviral therapy;
[a]*P*≤0.05 using two-tailed independent t-test.

Table 3. ADR reported in EPAS-ART

Month	Total ADR	Description of ADR
1	6	diarrhoea (n=2); lipodystrophy (n=1); dizziness (n=1); insomnia(n=1); vivid dream (n=1)
2	6	diarrhoea (n=2); lipodystrophy (n=1); dizziness (n=1); insomnia(n=1); vivid dream (n=1)
3	5	diarrhoea (n=2); dizziness (n=1); insomnia(n=1); vivid dream (n=1
4	4	diarrhoea (n=2); lipodystrophy (n=1); insomnia(n=1); vivid dream (n=1)
5	4	diarrhoea (n=2); lipodystrophy (n=1); insomnia(n=1); vivid dream (n=1)
6	4	diarrhoea (n=2);lipodystrophy (n=1);insomnia(n=1); vivid dream (n=1)

DISCUSSION

To the best of our knowledge, this is the first study in Malaysia to report medication adherence among patients receiving ART medications through the MDPS and to evaluate an intervention aimed at improving adherence in this population. Overall, baseline medication adherence in the study population was high, exceeding 99%. In ART, a minimum adherence level of 95% is required to achieve optimal therapeutic outcomes and treatment success.[16]

In contrast, a previous Malaysian study involving 242 patients receiving ART reported a lower adherence rate of 82.6%.[17] The difference may be attributed to differences in patient characteristics, as the earlier study involved ART-naive patients, whereas the mean duration of ART use in our study population was 4.53 years. Longer duration of ART has been associated with improved medication adherence among Asian populations, as patients become more accustomed to daily therapy, better understand the importance of ART, and experience a reduction in early ADR over time.[18] Consistent with this finding, several ADR reported initially in the present study were no longer reported at subsequent follow-ups.

Nevertheless, forgetfulness and being occupied with work commitments remain the most frequently cited reasons for non-adherence, regardless of the

duration of ART initiation.[19] Similarly, participants in our study commonly reported forgetting doses or being busy as reasons for missed medications.

Poor compliance or non-compliance with medication refills or pickups is a well-documented challenge among patients receiving ART. A qualitative study reported that frequent pharmacy visits may induce anxiety related to ART refills, and patients often forget their scheduled refill dates.[19] Strategies such as courier delivery of ART medications and telephone consultations were highly appreciated by patients.[19] In this context, remote monitoring and counselling interventions, such as EPAS-ART, are essential components of home medication delivery services, as they facilitate continuous communication with patients regarding medication use, enable timely education to prevent treatment discontinuation, and address adherence-related issues.

The findings of this study demonstrated an improvement in self-reported medication adherence from baseline to six months of follow-up in the EPAS-ART group. The EPAS-ART intervention involved structured pharmacist follow-ups addressing medication supply adequacy, missed doses and their reasons, as well as recent hospitalisations or emergency department visits. Evidence from a cross-sectional study involving 1,186 patients receiving erythropoiesis-stimulating agents through a medication delivery system revealed that approximately 30% of patients reported not receiving their medication, while 20% reported dosing errors and receipt of incorrect drugs.[20] These findings highlight the importance of pharmacist-led follow-up in medication delivery systems.

In addition, the EPAS-ART approach helps overcome common barriers such as stigma, transportation difficulties, and concerns regarding privacy, while offering greater feasibility and convenience by allowing patients to engage from their preferred environment. Although limited studies have examined telecare interventions among patients receiving home medication delivery service, a randomised study comparing standard hospital-based care with a virtual system for patients on home medication delivery services reported high patient satisfaction and reduced indirect costs in the virtual care arm.[21] However, no significant improvements were observed in ART adherence or other clinical parameters between the two care models.[21]

Limitations and Recommendation

Despite the novel implications of this study, several limitations should be acknowledged. Firstly, this was a single-centre study conducted in a tertiary referral hospital in Penang, which serves as a regional infectious disease centre for northern Malaysia, potentially limiting the generalisability of the findings to other healthcare settings. Secondly, medication adherence was assessed using self-reported pill counts, which may be subject to social desirability bias and could lead to an overestimation of adherence levels. Lastly, this study did not evaluate clinical outcomes such as viral load suppression or CD4 cell counts. Therefore, future studies should incorporate these clinical parameters to better demonstrate the impact of adherence on treatment outcomes.

CONCLUSION

The study results demonstrated no statistically significant difference in the change in self-reported medication adherence between the EPAS-ART and standard care groups. However, the intervention had an impact on maintaining optimum medication adherence among patients receiving ART medication delivered via MDPS with an early detection of ADR to the ART regimen.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest or financial relationships relevant to this article to disclose.

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ETHICAL APPROVAL

This study was registered with the National Medical Research Register of Malaysia (NMRR ID-20-3217-57124) and approved by the Medical Research Ethics Committee, Malaysia.

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