



(RESEARCH ARTICLE)



## The effect of number of pills and dosing frequency on antiretroviral drug adherence: An assessment using two adherence monitoring measures

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World Journal of Advanced Research and Reviews, 2022, 14(02), 253-260

Publication history: Received on 22 February 2022; revised on 09 April 2022; accepted on 11 April 2022

Article DOI: <https://doi.org/10.30574/wjarr.2022.14.2.0270>

### Abstract

**Background:** Strict adherence requirement to antiretroviral drugs remains a key determinant of successful treatment outcome. Drug regimen complexity has been identified as a factor that discourages adherence to antiretroviral therapy. Several measures are available to assess drug adherence each with its strengths and weaknesses. Only few of these measures are cost effective and can be used in resource limited settings.

**Objective:** To determine the effect of number of pills, dosing frequency, and concomitant drugs on adherence to antiretroviral drug therapy.

**Method:** This is a cross-sectional study utilizing a semi-structured questionnaire. Adherence to antiretroviral therapy was measured using self-report and prescription refill. The total number of pills and the dosing frequency were calculated and its association with poor adherence tested via a logistics regression model.

**Results:** Majority of the respondents were females (69.5%), aged 31-40 years (42.2%), married (68.5%), had greater than one pill in their drug regimen (84%), were on twice daily regimen (56.4%) and on other non-ARV drugs (59.9%).

An assessment of the adherence levels showed that 140(37.4%) and 161(43%) of the interviewed patients had poor adherence level of  $\leq 95\%$  as measured via self-report and pharmacy pick up respectively. At multivariate analysis taking other non-ARV drugs and taking 2 or more ARV pills were predictors of poor adherence to antiretroviral drugs (OR=9, 4.8-16.69) and (OR=0.19, 0.08-0.5) respectively.

**Conclusion:** The number of times drugs are taken in a day did not affect adherence in this study however, increased number of pills and addition of other concomitant medications to an antiretroviral regimen discouraged adherence.

**Keywords:** Antiretroviral therapy; Adherence measures; Self report; Prescription refill

### 1. Introduction

The need for near perfect adherence to highly active antiretroviral therapy (HAART) has remained a major pre-requisite to viral suppression and successful treatment outcome [1, 2]. The concept of adherence in the management of HIV infection is pertinent thus requires continuous monitoring and evaluation with respect to the patient and the drugs. Adherence levels below 95% have been termed sub-optimal and gives room for viral replication, drug resistance and consequently treatment failure [3, 4]. The complexity of antiretroviral drugs in terms of number of pills, food

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restrictions, cold storage requirements and dosing interval were a major Achilles heel of the earlier available antiretroviral formulations [5, 6]. They were characterized with several pills, multiple dosing times and for some of the initial protease inhibitor specifically Kaletra® soft gel capsules (Lopinavir/ritonavir), required refrigeration and this hampered to a great extent a patient's ability to cope and adhere to treatment. Antiretroviral drug formulations available for HIV treatment have evolved over the years in a bid to enhance adherence. The transition from the Lopinavir/ritonavir (133.3/33.3mg) soft gel co-formulation which required storage at 2-8°C to the 200/50 mg film coated co-formulation tablet that did not require cold storage put an end to the myriad of problems associated with the epileptic power supply which made it almost impossible to store and use this protease inhibitor in our environment [7].

The advent of fixed dose formulation was a major step taken to resolve adherence issues related to number of pills though not all drug combinations can be formulated as fixed dose formulation [8].

Co-morbidities and the development of opportunistic infections such as tuberculosis coupled with the requirement for cotrimoxazole or isoniazid prophylaxis among HIV infected individuals require additional treatment and this cannot be ignored [9, 10, and 11].

Efforts have been channeled towards reducing the complexity of antiretroviral drugs and simplifying HAART regimen however the need to address other health challenges with drug therapy which ultimately increases pill burden remains a major hurdle to addressing adherence issues [12].

Several measures have been developed to assess antiretroviral drug adherence each with its strength and weakness. Though no gold standard has been identified as a measure of adherence, methods such as self-report, pill counts, prescription refill, medication event monitoring system and biological assays have been used [13].

Self-report, pill counts, and pharmacy refill are methods that are cost effective in resource limited settings like ours. Since there is no perfect method, exploring and using at least two methods to assess adherence could help complement and confirm adherence results [3, 14].

In resource limited settings like ours it is imperative to ensure that antiretroviral therapy is adhered, to maintain patients on the first line regimen for as long as possible. The cost implication of a second and third-line regimen is much higher than that of a first line regimen [15]. As treatment complexity may interfere with patient's adherence it is necessary to investigate factors that could contribute to this as well as identify practical measures that can be used to monitor adherence. This study aims to determine the effect of number of pills dosing regimen, and concomitant drugs on adherence to antiretroviral drugs.

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## 2. Methodology

### 2.1. Study design

A cross sectional study utilizing an interviewer administered semi-structured questionnaire to obtain data from the respondents. Adherence was assessed using self-report and prescription refill measures.

### 2.2. Study setting

This study was carried out at the HIV treatment centre domiciled in the Clinical Sciences Department of the Nigerian Institute of Medical Research located in Lagos state, Nigeria. The HIV treatment centre has been in existence for over 18 years and has enrolled over 26,000 patients since inception. The clinic offers comprehensive HIV care to adults, paediatrics as well as prevention of mother to child transmission (PMTCT) services and post exposure prophylaxis treatment. Patients' data are stored in an electronic data base designed to document and monitor patient's drug pick up pattern. The clinic has a counselling unit charged with the responsibility of counselling HIV positive individuals on antiretroviral drug adherence. The pharmacy operates a system that allows a one-on-one interaction with the patients thereby allowing an assessment of each patient's adherence to medication on clinic visits. A one, two or three-month's supply of antiretroviral drugs is prescribed to individual patients based on certain defined criteria with corresponding clinical appointments for subsequent refill. The pharmacist monitors patient's adherence to these appointments communicates and refers default cases to the counselling unit for further counselling assessment and follows up.

### 2.3. Study Population

The study population comprises of 374 treatment experienced HIV positive adults who gave consent, had been on treatment for over a year and were aged above 18 years. Systematic sampling was used for patient selection during the study period from June to December 2019. We excluded pregnant women, children and those who did not give consent.

### 2.4. Adherence Assessment

#### 2.4.1. Self-report

Adherence using self-report entailed enquiring from the patient the number of doses they have missed in a month's regimen, in essence utilizing a 4-week recall. A non-judgemental approach was used in asking questions to allow patients give sincere responses and adherence was calculated by expressing the number of doses taken as a percentage of the total number of doses prescribed.

#### 2.4.2. Prescription Refill

Adherence assessment via prescription refill was calculated based on the assumption that prescription filled is prescription taken. Adherence was determined based on the patient's pick-up date thus the number of days off schedule in a patient's appointment was taken into consideration. Adherence calculation was by expressing the difference between the number of days from previous refill to visit date and the number of days off schedule as a percentage of the number of days from previous refill.

#### 2.4.3. Data Management

Data was collected using an interviewer administered semi-structured questionnaire; in addition, information on prescription refill was obtained from the clinic electronic data base. Adherence was calculated for each patient using the two measures and patients whose adherence were above or below 95% were termed good and poor respectively. Data obtained were entered into an excel spreadsheet and analyzed using SPSS Version 26. Descriptive analysis was carried out followed by multivariate analysis to determine factors associated with poor adherence.

#### 2.4.4. Ethical Considerations

Written informed consent was obtained from the respondents and those who declined to give consent were excluded from research but given care. Ethical approval for the study was obtained from the ethics committee of the institution.

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## 3. Results

During the seven months study period, a total of 374 patients were recruited and their socio-demographic characteristic is shown in Table 1. Majority were females (69.5%), of the age group 31-40 years (42.2%), married (68.5%), attained secondary level of education (47.1%) and are Christians (94.6%). Drug related factors describing level of adherence using the two different measures and a picture of drug types and dosing frequency has been portrayed in table 2.

Using the self-report method to measure adherence, showed that 62.6% of the patients achieved  $\geq 95\%$  while 57% achieved this using the prescription refill measure. Majority of the patients (84%) were taking more than 2 pills daily, on a twice daily regimen (56.4%), on other non-antiretroviral medications (59.9%) and are on the twice daily regimen of AZT/3TC/NVP (40.9%).

Table 3 shows the Multivariate analysis of some possible factors associated with poor adherence determined using outcome from self-report and prescription refill calculations. Factors such as 'taking other non-ARV drugs' ( $P < 0.001$ ), ( $O.R = 9(4.8-16.69)$ ) was associated with poor adherence using both measures of adherence. Taking '2 or more pills' was also found to be associated with poor adherence ( $p = 0.001$ ) ( $O.R = 0.19(0.08-0.5)$ ) specifically using the prescription refill measure.

**Table 1** Socio-demographic Characteristics of Respondents

Characteristics	Frequency N=374 (%)
<b>Sex</b>	
Male	114(30.5)
Female	260(69.5)
<b>Age</b>	
<30	68(18.2)
31-40	158(42.2)
41-50	102(27.3)
>50	46(12.3)
<b>Marital status</b>	
Single	78(20.9)
Married	256(68.5)
Widowed	26(6.9)
Divorced / Separated	14(3.7)
<b>Educational Status</b>	
Primary	80(21.3)
Secondary	176(47.1)
Tertiary	118(31.6)
<b>Religion</b>	
Christianity	354(94.6)
Islam	20(5.4)

**Table 2** Adherence assessment and drug related factors

Drug Related Factors	Frequency N=374(%)
<b>Self-Report</b>	
≥95% adherence(good)	234(62.6)
<95% adherence(poor)	140(37.4)
<b>Prescription refill</b>	
≥95% adherence(good)	213(57.0)
<95% adherence(poor)	161(43.0)
<b>No of Pills</b>	
1	60(16.0)
2-7	314(84.0)
<b>Dosing frequency</b>	
Once	163(43.6)
Twice	211(56.4)
<b>Other Non-ARV drugs</b>	
Yes	224(59.9)
No	150(40.1)

<b>Antiretroviral drug regimen</b>	
TDF/3TC/EFV	119(31.8)
AZT/3TC/NVP	153(40.9)
ABC/3TC +NVP	44(11.8)
ABC/3TC+EFV	16(4.3)
ATV/r+ TDF/3TC	40(10.7)
LPV/r + TDF/3TC	2(0.5)

**Table 3** Factors associated with poor adherence

<b>Variable</b>	<b>OR</b>	<b>P value</b>
<b>Self-report Measure</b>		
<b>Other Non-ARV Drugs</b>		
Yes	9(4.8-16.69)	<0.001
No	ref	
<b>Dosing frequency</b>		
Twice	1.36(0.81-2.29)	0.242
Once	ref	
<b>Number of Pills</b>		
2 or more	4.82(1.32-17.52)	0.017
1	ref	
<b>Prescription Refill Measure</b>		
<b>Other Non-ARV drugs</b>		
Yes	0.25(0.15-0.42)	<0.001
No	ref	
<b>Dosing Times</b>		
Twice	1.59(0.97-2.62)	0.068
Once	ref	
<b>Number of Pills</b>		
2 or more	0.19(0.08-0.5)	0.001
1	ref	

#### 4. Discussion

Assessing adherence to antiretroviral drugs is a necessary step to ascertain patient's progress with therapy. The fact that no perfect measure exists has given room for exploring more than one measure to give a clearer picture. This study has used two measures that are cost effective and readily available in our environment. Poor adherence levels (<95%) were observed in 37.4% and 43% of the patients using self-report and prescription refill measures respectively. This difference is expected because no two measures can give exact result as each measure has its strengths and weakness coupled with the fact that different criteria are considered in its calculation. However, the proximity of the values could help confirm and complement adherence results. Similarly, been and his colleagues [16], in Netherlands explored self-report and prescription refill. They demonstrated that both measures could predict undetectable viral load though the self-report measure had a higher specificity compared to pharmacy refill. Other researchers have compared a

combination of two or more adherence assessment methods which we didn't use in this study and have clearly demonstrated that no two measures give exact result but complement each other [13, 17].

The complexity of treatment regimen in terms of the number of pills, dosing frequency and additional non antiretroviral drugs was investigated in this study with respect to its association with poor adherence via a logistics regression model. It was observed that at multivariate analysis 'taking additional non antiretroviral drugs' had a very strong association with poor adherence (O.R = 9(4.8-16.69) as calculated using self-report as adherence measure. It was also observed to have an association with poor adherence using the prescription refill O.R = (0.25(0.15-0.42) though a stronger association was observed with self-report. This claim is buttressed by findings of Cantundo *et al* [18] whose study reported that patients on concomitant medications to address other health conditions besides HIV infection are prone to non-adherence to antiretroviral drugs. Furthermore, some researchers demonstrated that though the simplification of ARVs has helped in improving adherence, not all patients benefit from it as its effect can be counterbalanced by the effect on non-antiretroviral drugs taken by HIV positive individuals [19, 20].

This study revealed that taking two or more antiretroviral pills per day was associated with poor adherence compared to the single fixed dose regimen (O.R =0.19(0.08-0.5) though this fact was more depicted with the prescription refill assessment. Several studies [21, 22] have all demonstrated that the single dose regimen improved adherence. Incidentally, dosing frequency was not associated with poor adherence in our study. This is contrary to findings by Buscher [23] and his colleagues who reported greater adherence with once daily dosing compared with twice daily dosing frequency. Kapadia *et al* [24] also identified in their single pill regimens yielded better virological response compared to thrice daily regimen. The reason for this difference from our study might not be clear but a further qualitative study might throw more light on this.

It is also imperative for health workers to pay more attention to other co-morbid conditions and the corresponding treatment given to HIV positive individuals as this might help give a true picture of adherence to antiretroviral drugs.

#### *Limitation*

This study used two out of the several measures of adherence. The two measures are cost effective and are what will be readily available for use in a resource limited setting.

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## **5. Conclusion**

Adherence levels obtained using the two measures differed slightly. The number of times drugs are taken in a day did not affect adherence in this study but increased number of pills and addition of other concomitant medications to an antiretroviral regimen discouraged adherence.

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## **Compliance with ethical standards**

### *Acknowledgments*

We wish to acknowledge the participants of this study.

### *Disclosure of conflict of interest*

All authors declare no conflict of interest.

### *Statement of informed consent*

Written informed consent was obtained from the respondents and those who declined to give consent were excluded from research but given care.

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## **References**

- [1] Yu Y, Luo D, Chen X, Huang Z, Wang M, Xiao S. Medication Adherence to Antiretroviral Therapy among Newly Treated People Living with HIV, *BMC Public Health*. 2018; 18(1): 1–8.
- [2] Mbuagbaw L, Mertz D, Lawson DO, Smieja M, Benoit AC, Alvarez E, Ritchie LP, Rachlis B, Logie C, Husbands W, Margolese S, Thabane, L. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care for

- People Living with HIV in High-Income Countries: A Protocol for an Overview of Systematic Reviews, *BMJ Open*. 2018; 8(9): e022982.
- [3] Iacob SA, Iacob DG, Jugulete G Improving the Adherence to Antiretroviral Therapy, a Difficult but Essential Task for a Successful HIV Treatment-Clinical Points of View and Practical Considerations, *Frontiers in Pharmacology*. 2017; 23;8:831. doi: 10.3389/fphar.2017.00831.
- [4] Kim J, Lee E, Park B, Bang JH, Lee JY. Adherence to Antiretroviral Therapy and Factors Affecting Low Medication Adherence among Incident HIV-Infected Individuals during 2009-2016: A Nationwide Study, *Scientific Reports*. 2018; 8(1): 1–8.
- [5] Katy A. Van Galen, Jeannine F. Nellen, Pythia T. Nieuwkerk, The Effect on Treatment Adherence of Administering Drugs as Fixed-Dose Combinations versus as Separate Pills: Systematic Review and Meta-Analysis, *AIDS Research and Treatment*. 2014; Article ID 967073, 6 pages <http://dx.doi.org/10.1155/2014/967073>
- [6] Oh KS, Seo H, Choi HK, Han E. Effect of Single Tablet Regimen on Prescription Trends for Treatment-Naïve Patients with HIV/AIDS in Korea, *Scientific Reports*. 2022; 12(1): 1–8.
- [7] Chandwani A, Shuter J. Lopinavir/Ritonavir in the Treatment of HIV-1 Infection: A Review, *Therapeutics and Clinical Risk Management*. 2008; 4(5): 1023–33.
- [8] Armstrong B, Chan DJ, Stewart MJ, Fagan D, and Smith D Single Tablet Regimen Usage and Efficacy in the Treatment of HIV Infection in Australia, *AIDS Research and Treatment*. 2015; 570316. <https://doi.org/10.1155/2015/570316>
- [9] Dembelu M and Woseneleh T. Prevalence of and Factors Associated with Reoccurrence of Opportunistic Infections among Adult Hiv/Aids Patients Attending the Art Clinic at Public Health Facilities in Arba Minch Town, Southern Ethiopia, *HIV/AIDS - Research and Palliative Care*. 2021; 13: 867–76.
- [10] Sisay M, Bute D, Edessa D, Mengistu G, Amare F, Gashaw T, Bihonegn T. Appropriateness of Cotrimoxazole Prophylactic Therapy among HIV/AIDS Patients in Public Hospitals in Eastern Ethiopia: A Retrospective Evaluation of Clinical Practice, *Frontiers in Pharmacology*. 2018; 9: 1–9.
- [11] Legese H, Degefa H, Gebrewahd A, Gebremedhin H. Utilization of Isoniazid Prophylaxis Therapy and Its Associated Factors among HIV Positive Clients Taking Antiretroviral Therapy at Fre Semaetat Primary Hospital, Hawzien Districts, Tigray, Northern Ethiopia, *Tropical Diseases, Travel Medicine and Vaccines*. 2020; 6(1): 2–8.
- [12] Kessler HH, Stelzl E, Blazic A, Mehta SR, Benezeder AS, Genger-Heckle C. Antiretroviral Treatment Simplification with 2-Drug Regimens: Impact of Transmitted Drug Resistance Mutations, *Open Forum Infectious Diseases*. 2020; 7(1): 5–8.
- [13] Orrell C, Cohen K, Leisegang R, Bangsberg DR, Wood R, Maartens G Comparison of Six Methods to Estimate Adherence in an ART-Naïve Cohort in a Resource-Poor Setting: Which Best Predicts Virological and Resistance Outcomes?, *AIDS Research and Therapy*. 2017; 14(1): 1–11.
- [14] Zied Gaifer and Mohamed Rachid Boulassel, Comparative Analysis of Two Methods of Measuring Antiretroviral Therapy Adherence in HIV-Infected Omani Patients, *Journal of the International Association of Providers of AIDS Care*. 2019; 18(2063): 1–6.
- [15] Nega J, Taye S, Million Y, Eshetie S. Antiretroviral Treatment Failure and Associated Factors among HIV Patients on First-Line Antiretroviral Treatment in Sekota, Northeast Ethiopia, *AIDS Research and Therapy*. 2020; 17(1): 1–9.
- [16] Been SK, Yildiz E, Nieuwkerk PT, Pogany K, van de Vijver D, Verbon A. Self-Reported Adherence and Pharmacy Refill Adherence Are Both Predictive for an Undetectable Viral Load among HIV-Infected Migrants Receiving CART, *PLoS ONE*. 2017; 12(11): 1–12.
- [17] Sumari-de Boer IM, Ngowi KM, Sonda TB, Pima F, Masika LV, Sprangers MA. Effect of Digital Adherence Tools on Adherence to Antiretroviral Treatment Among Adults Living With HIV in Kilimanjaro, Tanzania: A Randomized Controlled Trial, *Journal of Acquired Immune Deficiency Syndromes (1999)*. 2021; 87(5): 1136–44.
- [18] Cantudo-Cuenca MR, Jiménez-Galán R, Almeida-Gonzalez CV, Morillo-Verdugo R. Concurrent Use of Comedications Reduces Adherence to Antiretroviral Therapy among HIV-Infected Patients, *Journal of Managed Care Pharmacy*. 2014; 20(8): 844–50.

- [19] Giraud JS, Doisne M, Chan Hew Wai A, Majerholc C, Fourn E, Sejean K, Trichereau J, Bonan B, Zucman D De-Simplifying Single-Tablet Antiretroviral Treatments for Cost Savings in France: From the Patient Perspectives to a 6-Month Followup on Generics, *PLoS ONE*. September 2020; 15(9): 1–12.
- [20] Kanters S, Park JJ, Chan K, Socias ME, Ford N, Forrest JI, Thorlund K, Nachega JB, Mills EJ. Interventions to Improve Adherence to Antiretroviral Therapy: A Systematic Review and Network Meta-Analysis, *The Lancet HIV*. 2017; 4(1): e31–40,
- [21] Tennant SJ, Hester EK, Caulder CR, Lu ZK, Bookstaver PB. Adherence among Rural HIV-Infected Patients in the Deep South: A Comparison between Single-Tablet and Multi-Tablet Once-Daily Regimens, *Journal of the International Association of Providers of AIDS Care*. 2015; 14(1): 64–71.
- [22] Clay PG, Yuet WC, Moecklinghoff CH, Duchesne I, Tronczyński KL, Shah S, Shao DA A Meta-Analysis Comparing 48-Week Treatment Outcomes of Single and Multi-Tablet Antiretroviral Regimens for the Treatment of People Living with HIV, *AIDS Research and Therapy*. 2018; 15(1): 1–10.
- [23] Buscher A, Hartman C, Kallen MA, Giordano TP Impact of Antiretroviral Dosing Frequency and Pill Burden on Adherence among Newly Diagnosed, Antiretroviral-Naïve HIV Patients, *International Journal of STD and AIDS*. 2012; 23(5): 351–55.
- [24] Kapadia SN, Grant RR, German SB, Singh B, Davidow AL, Swaminathan S, Hodder S. HIV Virologic Response Better with Single-Tablet Once Daily Regimens Compared to Multiple-Tablet Daily Regimens, *SAGE Open Medicine*. 2018; 6: 205031211881691.