The Mean Levels of Adherence and Factors Contributing to Non-adherence in Patients on Highly Active Antiretroviral Therapy

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ABSTRACT

Objective: To determine the mean level of adherence and factors contributing to non-adherence in patients on Highly Active Antiretroviral Therapy (HAART).

Methods: An observational study was done on 101 HIV/AIDS patients attending the Centre for HIV/AIDS Research, Education and Services (CHARES) – University Hospital of the West Indies, between May 2006 and August 2006. A questionnaire was administered asking questions re: prescribed and actual dosing frequency and number of antiretroviral tablets for the previous week, reasons for non-adherence, duration of Highly Active Antiretroviral Therapy, age, employment status and level of education. Mean levels of adherence were calculated using self and social worker/nurse reported dosing frequency and number of tablets. Good adherence was defined as 95% or greater. Multiple regression analysis was used to determine factors impacting on adherence.

Results: Ninety-six patients were included for final analysis. Mean levels of adherence were as follows: 87.66% – self-report for tablets; 88.70% – self-report for dosing frequency; 87.02% – social worker/nurse report for tablets; 88.10% – social worker/nurse report for dosing frequency. There were significant positive correlations between self and social worker/nurse reports using dosing frequency (Spearman Rho correlation coefficient 0.943, p = 0.01) or number of tablets (Spearman Rho correlation coefficient 0.955, p = 0.01). Adherence to self-reported number of tablets and dosing frequency were 58.4% and 56.4% respectively. Duration of HAART was found to have a significant negative correlation with the level of self-reported adherence to tablets (p = 0.002).

Conclusion: Adherence to HAART is sub-optimum in patients at the CHARES. This must be urgently addressed to prevent the development of resistant HIV strains and treatment failure.

Niveles Medios de Adhesión y Factores que Contribuyen a la no Adhesión en Pacientes Bajo Terapia Antiretroviral Altamente Activa

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RESUMEN

Objetivo: Determinar el nivel medio de adhesión y los factores que contribuyen a la no adhesión en pacientes bajo terapia antiretroviral altamente activa (TARAA).

Métodos: Se realizó un estudio observacional a 101 pacientes con VIH/SIDA, que asistían al Centro de Investigación, Educación y Servicios de VIH/SIDA (CHARES), del Hospital Universitario de West Indies, entre mayo del 2006 y agosto del 2006. Se administró una encuesta con preguntas sobre la frecuencia de la dosificación prescrita y real y el número de tabletas antiretrovirales para las razones de la semana previa para la duración de la no adhesión al TARAA, la edad, el estatus de empleo y el nivel de educación. Los niveles medios de adhesión fueron calculados usando frecuencias de dosificación auto-reportadas, o reportadas por enfermeras o trabajadoras sociales, y el número de tabletas. Una adhesión era definida como buena si alcanzaba el 95% o más. Para determinar los factores que tienen un impacto sobre la adhesión se recurrió al análisis de regresión múltiple.

Resultados: Noventa y seis pacientes fueron incluidos en el análisis final. Los niveles medios de adhesión fueron los siguientes: 87.66% – auto-reportes de tabletas; 88.70% – auto-reportes de frecuen-cia

de dosificación; 87.02% reportes de tabletas por enfermeras o trabajadoras sociales; 88.10% reportes de frecuencia de dosificación por parte de enfermeras o trabajadoras sociales. Hubo correlaciones positivas significativas entre los auto-reportes y los reportes de las enfermeras y traba-jadoras sociales que usaron frecuencia de dosificación (coeficiente de correlación rho de Spearman 0.943, p = 0.01) *o número de tabletas (coeficiente de correlación rho de Spearman 0.955,* p = 0.01). *Según los auto-reportes, la adhesión al número de tabletas y a la frecuencia de dosificación fueron 58.4% y 56.4% respectivamente. Se halló que la duración del TARAA tiene una correlación negativa significativa con el nivel auto-reportado de adhesión a las tabletas* (p = 0.002).*

Conclusión: *La adhesión a la Terapia Antiretroviral Altamente Activa es sub-óptima en los pacientes del Centro CHARES. Esto es algo que requiere atención urgente si se quiere prevenir el desarrollo de cepas resistentes de VIH y el fracaso del tratamiento.*

INTRODUCTION

The introduction of Highly Active Antiretroviral Therapy (HAART) has reduced significantly the mortality and morbidity associated with HIV/AIDS in the pre-HAART era but has generated new concerns about the development of multi-drug resistant strains of HIV. Given the limited number of antiretrovirals, fighting resistance to antiretrovirals is fast becoming the new challenge in this HIV pandemic. Furthermore, studies have shown that the first HAART regimen has the best chance for long-term success**.**

Adherence of patients to HAART regimens is therefore critical in preventing the development and transmission of resistant strains. Second and third line HAART regimens are usually more expensive than first line regimens used in developing countries such as Jamaica. The cost for phenotypic and genotypic resistance testing is prohibitive to most individuals in the public health setting. Therefore, in most cases, it can only be surmised that treatment failure would be the result of viral resistance and second and third line regimens empirically instituted for such patients.

The issue now arise on how to measure adherence. Depending on which measures are used, a patient may have conflicting levels of adherence (1). Direct Observation Therapy (DOT) may be considered the gold standard for measurement of adherence to HAART but is far from ideal since most regimens involve multiple daily doses which make DOT impractical. Self-reporting and medication event monitoring systems (MEMS) are among the most reliable measures (1–6). However, patients tend to overestimate adherence. The use of pill-sorters, by many patients, makes MEMS redundant in measuring adherence. Physician-reporting and pill-counts have been found to be among the least reliable measures (3).

The Centre for HIV/AIDS Research, Education and Services (CHARES) at the University Hospital of the West Indies provide care to over five hundred patients who are HIV positive. These are patients from diverse cultural, educational and socioeconomic backgrounds, factors that may impact significantly on adherence. The determination of levels of adherence and the factors affecting non-adherence in these patients will contribute greatly to the clinical approach and the development of programmes to improve adherence.

SUBJECTS AND METHODS

This was an observational study that was done on patients attending the CHARES outpatient clinics, University Hospital of the West Indies, between May 2006 and August 2006. All patients who attended the clinic during this period were invited to participate. A questionnaire was developed to calculate patient adherence based on dosing frequency and number of tablets and to determine factors which may influence adherence. Patients were asked to add factors, not listed in the questionnaire, which they thought contributed to their non-adherence. Data on age, level of education, employment status and duration of HAART for each patient were noted. Adherence was calculated based on the following formulae:

1. Number of tablets:

$$\frac{\text{Total number of tablets taken in the past one week}}{\text{Total number of tablets due in the past one week}} \times 100$$

Total number of tablets taken = Total number of tablets due – Total number of tablets missed (all within the past one week)

Total number of tablets due in the past week = number of tablets due per day $\times$ 7

2. Number of doses:

$$\frac{\text{Total number of doses taken in the past one week}}{\text{Total number of doses due in the past one week}} \times 100$$

Total number of doses taken = Total number of doses due – Total number of doses missed (all within the past one week)

Total number of doses due in the past week = dosing frequency $\times$ 7

Dosing frequency = number of times per day tablets are taken

Patients were asked to complete the questionnaire on their own to measure self-reported adherence. When necessary, the questions were explained and patients could verify which tablets they were on, how many and the intended dosing frequency. An identical questionnaire was administered by a social worker/nurse. Therefore, each patient had both self-report and social worker/nurse-based report; and for each report, adherence was measured using dosing frequency and number of tablets due in the past one week. Good adher-

ence was defined as 95% or greater and patients with lower than 95% adherence were classified as being non-adherent (7).

Mean levels of adherence were determined for self-reported tablets, self-reported dosing frequency, social worker/nurse-reported tablets and social worker/nurse-reported dosing frequency. Spearman Rho analysis was used to assess correlation between self and social worker/nurse-reported tablets; and between self and social worker /nurse-reported dosing frequency. Influence of factors on adherence was assessed using multiple regression analysis.

RESULTS

A total of 101 patients was enrolled in the study but five were excluded from the final analysis due to insufficient information. Of the remaining subjects, 45.80% (n = 44) and 54.20% (n = 52) were male and female respectively. Their ages ranged from 20 to 58 years.

The mean ages for men and women were 35.85 years and 35.39 years respectively. Duration of HAART ranged from 2 weeks to 192 months and the mean duration of HAART was 24.62 months. The employment rate among patients was 50.5%. Patients attaining education at the primary, secondary and tertiary levels were 16.1%, 60.2% and 23.7% respectively (Table 1).

Table 1:   Patient characteristics

Parameter	Result
Gender	45.8% – male (n = 44); 54.2% – female (n = 52)
Mean age	35.85 years – male; 35.39 years – female
Mean duration of HAART	24.62 months
Employment status	50.5% employed
Level of education	primary: 16.1% secondary: 60.2% tertiary: 23.7%

The mean adherence to tablets by self-report was 87.66%, SD ± 24.799 and mean adherence to dosage by self-report was 88.70%, SD ± 24.521. The mean adherence to tablets by social worker/nurse-report was 87.02%, SD ±

24.395 and mean adherence to dosage by social worker/nurse-report was 88.10%, SD ± 23.753 (Table 2).

With respect to self-reported adherence to tablets and dosing frequency, 58.4% and 56.4% were adherent respectively. Using self-reported adherence to tablets, 9.4% of patients had 50% or less adherence (Fig. 1–2).
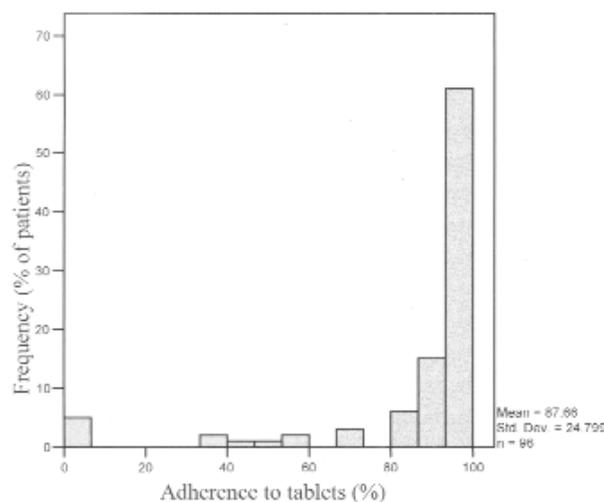

Fig. 1:   Frequency of self-reported adherence to tablets.

There was a significant positive correlation between self-reported adherence to tablets and social worker/nurse-reported adherence to tablets ($p = 0.01$, Spearman's Rho correlation coefficient 0.955). Also, there was a significant positive correlation between self-reported adherence to dosage and social worker /nurse-reported adherence to dosage ($p = 0.01$, Spearman's Rho correlation coefficient 0.943).

A number of factors contributing to non-adherence was investigated. The most frequent reasons cited were leaving tablets at home (24.6%) and forgetting to take tablets (21.1%). The fear of side-effects only accounted for 3.5% (Fig. 3).

Duration of HAART was found to have a significant negative correlation with the level of self-reported adherence to tablets using multiple regression analysis ($p = 0.002$). No

Table 2:   Mean adherence of self and social worker/nurse – reports using dosing frequency and number of tablets for measuring adherence

| Statistical parameter	Adherence to tablets, sw	Adherence to dosage, sw	Adherence to tablets, self	Adherence to dosage, self
Number of subjects included	89	89	96	94
Number of subjects excluded	12	12	5	7
Mean	87.02	88.10	87.66	88.70
Std Error of Mean	2.586	2.518	2.531	2.529
Median	100.00	100.00	100.00	100.00
Mode	100	100	100	100
Std Deviation	24.395	23.753	24.799	24.521
Minimum	0	0	0	0
Maximum	100	100	100	100

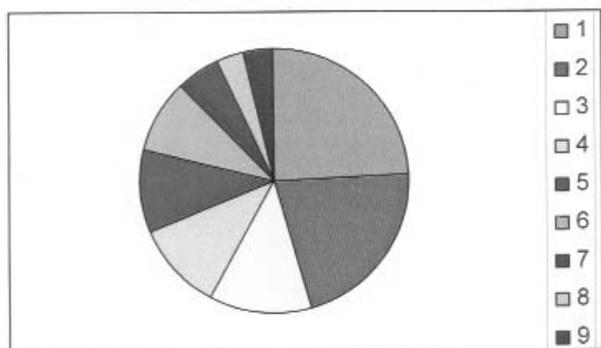sw = social worker/nurse, std = standard
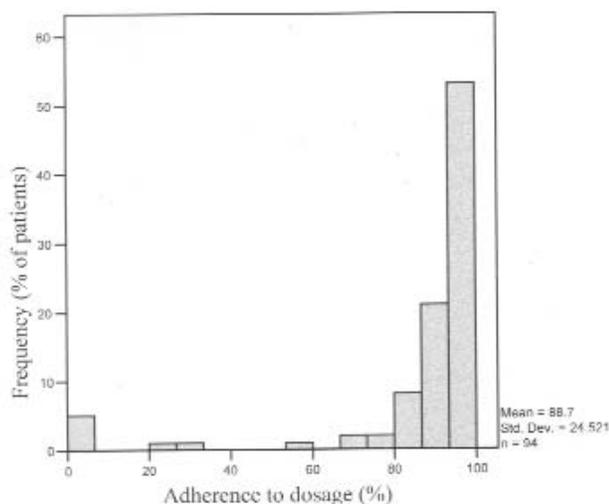
Fig. 2:   Frequency of self-reported adherence to dosage.

1. Mistakenly left tablets at home or work, 2. forgot to take tablets, 3. tablets were finished, 4. miscellaneous, 5. fell asleep, 6. no food, 7. tired of tablets, 8. fear of side-effects, 9. social problems.

Fig. 3:   Reasons for self-reported non-adherence to HAART

other factors including age, gender, employment status and level of education were found to be associated with level of self-reported adherence to tablets. None of the above noted factors, including duration of HAART ($p = 0.071$), were found to be significant when self-reported adherence to dosage was used as the dependent variable (Table 3).

DISCUSSION

The lack of standardized techniques to measure adherence to HAART is an issue that plagues many studies of this nature (3, 8). Multiple measures of adherence were used, recognizing that for any given patient he/she could have different levels of adherence depending on which parameter is used to measure adherence (Table 2). Except when a patient has 100% adherence, dosing frequency and number of tablets may produce different levels of adherence even when correct and consistent data are given by the patient.

A common scenario is a patient on one tablet twice daily of combined lamivudine/zidovudine and one tablet of efavirenz at nights who takes both evening tablets at the same time. The daily dosing frequency would be two while the daily number of tablets taken would be three. If this patient were to omit efavirenz but continue to take lamivudine/zidovudine twice daily, adherence when measured by dosing frequency will be 100% but will be only 66.7% when adherence is measured using number of tablets.

Measurement of adherence using number of tablets is clearly more accurate but many patients, on multiple daily doses of up to 10 tablets per day or more, may not remember how many tablets they missed. It is often easier to remember how many times they missed taking their medications but this may not be accurate as outlined above. For this study, adherence was measured in these different ways recognizing that the use of adherence to number of tablets should in most cases be a more accurate reflection of the true level of patient adherence.

There was a significant positive correlation between self-reported adherence to tablets and social worker /nurse-reported adherence to tablets. The association between self and social worker /nurse-reports also held true when adherence to dosage was used. Many previous studies have validated the use of self-report as a reasonable measure of adherence but have found unreliable, third person reports such as physician- and nurse-based reports (3, 9).

There is a high reliability on patient information in most adherence studies. The use of independent data such as MEMS and DOT are also far from infallible and self-report has indeed been shown to be a practical and a fairly reliable measure of adherence (4, 5, 6). Self-report has been shown

Table 3:   Multiple regression analysis of factors influencing self-reported adherence to tablets

Model	Unstandardized coefficients		Standardized coefficients		
	B	Std Error	Beta	t	Sig
Constant	98.241	23.181		4.238	0.000
Numeric duration of HAART in months	-0.349	0.108	-0.356	-3.242	0.002
Employment status	-3.673	6.942	-0.059	-0.529	0.598
Age	-0.069	0.414	-0.019	-0.166	0.868
Gender numeric	11.465	7.019	0.184	1.633	0.107
Level of education	-6.704	5.903	-0.128	-1.136	0.260

to correlate well with virologic and immunological response to therapy (5, 6). The level of adherence was not correlated to viral load or CD4 count and this was a significant limitation of this study. Further studies on adherence should address this aspect.

The percentage adherence (58.4% for self-reported adherence to tablets and 56.4% for self-reported adherence to dosing frequency) and the mean levels of adherence are consistent with the findings of other studies done in similar patient populations. A meta-analysis of adherence studies done in Africa and North America, in which self-reported adherence was utilized in 71% of the North American sites and 66% of the African sites, showed adequate adherence in 55% of patients in North America and 77% of those in Africa (10).

A significant number of patients are at high risk for treatment failure due to lack of viral suppression caused by non-compliance, with or without the development of anti-retroviral resistance. It is important that these patients be identified and measures taken to improve their adherence.

Overall, the most frequent reasons for non-adherence were: leaving tablets at home or work, forgetting to take tablets and running out of tablets (Fig. 3). Physicians, social workers and adherence officers should seek to address these during patient interviews and adherence clinics.

Duration of HAART was found to have a significant negative correlation with self-reported level of adherence to tablets. This is important to know since HAART is a lifelong treatment. No other factors that were evaluated, including age, gender, employment status and level of education were found to be associated with the level of adherence.

In summary, the mean levels of adherence at CHARES are sub-optimum. The impact of duration of HAART on adherence has special significance since HAART is a lifelong therapy. Adherence is arguably the greatest determinant of the success of HAART. The development of resistant strains of HIV has the potential to overwhelm existing drugs and those in development. Ensuring adherence, by the rational development of programmes for the delivery of healthcare, is the best and most cost-effective weapon against multi-drug resistant HIV.

REFERENCES
1. Vincke J, Bolton R. Therapy adherence and highly active antiretroviral therapy: comparison of three sources of information. AIDS Patient Care STDS 2002; **16**: 487–95.
2. Hardy H. Adherence to antiretroviral therapy: The emerging role of HIV pharmacotherapy specialists. J Pharm Prac 2005; **18**: 247–57.
3. Cinti S K. Adherence to antiretrovirals in HIV disease. AIDS Read 2000; **10**: 709–17.
4. Stone VE. Monitoring and measuring adherence to HAART in clinical practice. Medscape General Medicine 2002; **4(3)**. Available at: *http://www.medscape.com/voewartoc;e/438193_5*. Accessed March 21, 2006.
5. Nieuwkerk PT, Oort FJ. Self-reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: a meta-analysis. J Acquired Immune Defic Syndr 2005; **38**: 445–8.
6. Haubrich RH, Little SJ, Currier JS, Forthal DN, Kemper CA, Beall GN, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. AIDS 1999 Jun 18; **13**: 1099–107.
7. Paterson D L, Swindells S, Mohr J, Brester M, Vergis E N, Squier C et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000; **133:** 21–30.
8. Liu H, Golin CE, Miller LG, Hays R D, Beck CK, Sanandaji S et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med 2001; **134:** 968–77.
9. Murri R, Ammassari A, Trotta MP, De Luca A, Melzi S, Minardi C et al. Patient-reported and physician-estimated adherence to HAART: social and clinic center-related factors are associated with discordance. J Gen Intern Med 2004; **19:** 1104–10.
10. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S et al. Adherence to antiretroviral therapy in Sub-Saharan Africa and North America: A meta-analysis. JAMA 2006; **296:** 679–90.