

ORIGINAL RESEARCH

Long-term utility of measuring adherence by self-report compared with pharmacy record in a routine clinic setting

CK Fairley,[1,2] A Permana[2] and TRH Read[1]

[1]*Melbourne Sexual Health Centre, and* [2]*School of Population Health, University of Melbourne, Melbourne, Victoria, Australia*

Objectives

To compare long-term adherence to antiretroviral therapy in an HIV service, as measured by self-report and by pharmacy records. To determine the level of adherence by each measure required to suppress viral load in a majority of patients.

Methods

The percentage of prescribed doses taken was calculated from (a) the number of missed doses in the previous 28 days reported by patients in a questionnaire at each clinic visit, and (b) pharmacy dispensing records. These were compared with each other and with HIV viral load data.

Results

Mean adherence was 96.2% by pharmacy record over 44 months and 98.6% by self-report over 25 months. The two methods correlated with each other ($P<0.001$) and the proportion of patients with viral load <400 HIV-1 RNA copies/mL increased with adherence as measured by self-report ($P=0.001$) and pharmacy record ($P=0.004$). Fewer than 60% of patients always had viral loads <400 copies/mL if adherence fell below 95% (pharmacy record) or 97% (self-report). Adherence was higher for once-daily than for twice-daily therapy (by pharmacy record: 97.2% vs. 96.0%; $P<0.001$). Adherence by both measures increased over time.

Conclusions

Self-reported antiretroviral adherence correlates with pharmacy dispensing records and predicts suppression of viral load at levels $\geq$ 97%. It is practical to adopt this into routine HIV clinical care.

Keywords: adherence, antiretroviral therapy, compliance

Received: 28 September 2004, accepted 9 March 2005

Introduction

One of the most important issues in managing patients with HIV therapy is adherence to this therapy [1]. Extraordinarily high levels of adherence, of greater than 95%, need to be achieved and maintained for many years if treatment is to be successful and the development of resistance is to be prevented [2]. Not only are these levels much higher than are needed for other chronic conditions such as hypertension, but even temporary failure to adhere carries the risk of long-term treatment failure [2]. Clinical guidelines recommend, among other things, measuring adherence regularly, and in most clinics self-report is the only feasible method [2]. Because most studies have taken place over short periods and are not necessarily generalizable to a standard HIV service, it remains unclear what level of self-reported adherence is sufficient [3].

To answer this question, we assessed the results at our clinic, where we have measured adherence at every clinical visit since May 2001. We have noticed that a significant proportion of patients are reporting 100% adherence but have a detectable viral load [4]. Our aim was to determine what level of self-reported adherence was associated with a decline in viral load and to compare this to another measure of adherence.

Methods

This was a retrospective audit undertaken at the HIV clinic at Melbourne Sexual Health Centre. This clinic provides free

Correspondence: Christopher K. Fairley, Melbourne Sexual Health Centre, 580 Swanston Street, Carlton, Victoria 3053, Australia. Tel: 61 39341 6236; fax: 61 3347 6757; e-mail: cfairley@unimelb.edu.au

antiretroviral therapy and dispenses over 50% of all antiretroviral therapy in Victoria. Because other centres in Melbourne charge $23.80 per item per month, patients at MSHC frequently return to this centre for every prescription.

Adherence was measured by two methods: self-reported adherence and an audit of pharmacy records. Self-reported adherence was measured from May 2001 to August 2003 by the Every Visit Adherence Questionnaire of the clinic. At each clinic visit, patients record their number of daily doses and the number of doses they missed over the last 28 days [4]. Adherence was calculated as the percentage of doses taken over each period. For each individual, the average adherence was calculated for the period for which data were available. Self-reported adherence was only available for patients who were seen by practitioners in the clinic. About half of the patients who receive therapy from our pharmacy are seen and have prescriptions written elsewhere.

Adherence using pharmacy record was measured by using the pharmacy computerized dispensing system (STOCCA) from January 2000 until August 2003. For each patient, the number of days of therapy prescribed (excluding the last prescription) was divided by the number of days between the first and last prescriptions. Adherence levels of more than 100% were rounded down to 100%. Drugs were excluded from the analysis if they did not have a standard dose, the dose varied or they were prescribed infrequently. Drugs that were included in the analysis were: abacavir 300 mg, didanosine 100, 250 and 400 mg, efavirenz 200 and 600 mg, lamivudine 150 mg, Combivir (zidovudine and lamivudine, GSK, Brentford, UK), nevirapine 200 mg, stavudine 30 and 40 mg, Trizivir (abacavir, zidovudine and lamivudine, GSK), tenofovir 300 mg, zidovudine 250 mg, and lopinavir. Patients were excluded from the analysis if there was a gap of more than 6 weeks in their medication supply as these patients were considered more likely to have obtained medication elsewhere, or to have stopped their treatment. Once a day treatment was defined as those drugs licensed as once a day at the time of the study (tenofovir, didanosine 250 and 400 mg, and efavirenz).

Viral load and CD4 lymphocyte counts were obtained from the electronic data records of the clinic. When viral load measurements were compared with adherence, the average adherence over the entire period was compared with the proportion of patients who always had a viral load of less than 400 HIV-1 RNA copies/mL over the entire period.

Analysis

Multiple linear regression was used to determine if the adherence had changed over the 4-year period, taking account of repeated measures for each year and once vs twice a day treatment. A *t*-test, a χ^2 test or McNemar's test were used for other comparisons depending on whether the data were continuous or categorical.

Results

Pharmacy record

Between January 2000 and August 2003, 880 patients received prescriptions for at least one of the selected antiretroviral drugs through the MSHC pharmacy. Of these, 128 individuals were excluded because they had gaps in their prescriptions of 6 weeks or more. The mean adherence over this time was 96.2% and adherence increased significantly each year ($P = 0.03$, Table 1). Adherence was significantly higher for once a day compared with twice a day treatment (97.2% vs. 96.0%; $P < 0.001$; Table 2).

Self-report

Between May 2001 and August 2003 there were 488 patients who attended the clinic and were taking antiretrovial therapy, and who completed the Every Visit Adherence Questionnaire. Their mean age was 43 years, 464 were male, 449 were men who had sex with men and seven were injecting drug users. The mean adherence of these 488 individuals was 98.6% and the median was 99.7% (range 50% to 100%). The mean adherence increased significantly between 2001 and August 2003 ($P = 0.005$; Table 1).

Viral load correlation

The viral load measurements were significantly related to adherence measured by both pharmacy record and self-report ($P < 0.004$) (Fig. 1). The proportion of patients with viral load below 400 copies/mL fell below 60% when adherence fell below 95% (by pharmacy record) and 97% (by self-report).

Table 1 Adherence by year of treatment from pharmacy record (PR) and self-report (SR)

Year	Mean PR (SD)	25th percentile PR	Mean SR (SD)	25th percentile SR
2000	95.6 (6.4)	92.2		
2001	96.2 (6.1)	94.2	98.1 (3.3)	98.2
2002	96.3 (6.1)	95.0	98.7 (3.0)	99.3
2003	96.6 (6.0)	95.6	99.0 (3.2)	100

Mean adherence (repeated measures) adjusted for times per day increased significantly over time for pharmacy record ($P = 0.03$) and self-report ($P = 0.005$).
SD, standard deviation.

Table 2 Adherence for once a day regimens compared with twice a day by pharmacy record

Mean (SD)	25th percentile	
Once a day	97.2 (5.4)	96.8
Twice a day	96.0 (6.3)	93.8
Total	96.2 (6.2)	

$P<0.001$ for mean adherence, for once a day compared with twice a day. There were 378 patients taking at least one once a day treatment, and 749 patients taking at least one twice a day treatment.
SD, standard deviation.

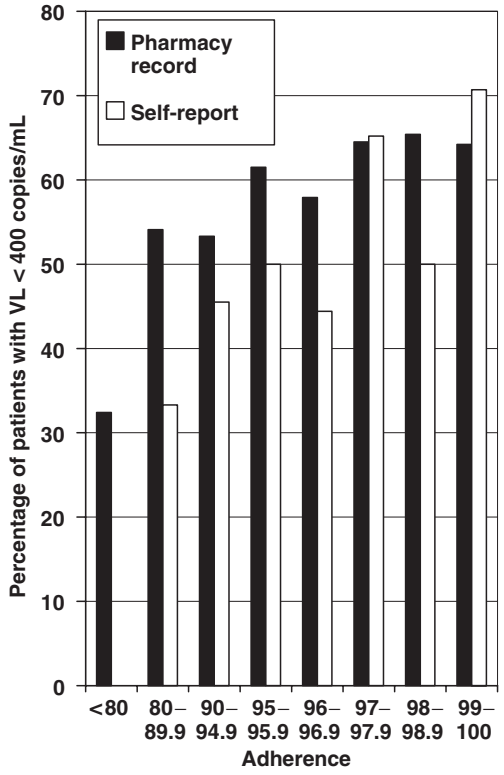

Fig. 1 Percentage of patients with viral load (VL) <400 copies/mL at increasing levels of adherence by pharmacy record or self-report. Defined as the percentage with VL below 400 copies/mL for all measurements in any one individual. Self-reported adherence ($P = 0.001$) and pharmacy record adherence ($P = 0.004$ by χ^2 test) both significantly increased as the percentage with undetectable VL rose.

Correlations between adherence measures

Table 3 shows the correlation between self-report and pharmacy record, using $<95\%$ as nonadherent for pharmacy record and $<97\%$ as nonadherent for self-report. Pharmacy record identified about twice as many individuals as nonadherent compared with self-report (27% vs. 14%; $P<0.001$).

Table 3 Self-reported adherence compared with pharmacy record

	Adherence (pharmacy record)		
	$<95\%$	$\geq 95\%$	Total
Adherence (self-report)			
$<97\%$	29	30	59
$\geq 97\%$	83	272	355
Total	112	302	414

Discussion

This study of adherence to antiretrovirals in routine clinical care found higher levels of adherence when adherence was measured by patient self-report (mean 98.6%) than when it was measured by pharmacy dispensing records (mean 96.2%). The proportion of patients with viral load consistently <400 copies/mL fell below 60% at a higher level of adherence as measured by self-report (97%) than as measured by pharmacy records (95%). Pharmacy records also showed that once-daily dosing was associated with higher levels of adherence than twice-daily dosing, and adherence measured by both methods increased over time.

We measured long-term adherence by two practical, inexpensive methods, self-report (2 years 3 months) and pharmacy records (3 years 8 months), and found clinically useful levels of adherence required to suppress viral load in most patients. Electronic measurements such as MEMS (Medication Event Monitoring System, Aprex Corp., Fremont, CA, USA) caps are more accurate measures of adherence, but are too expensive for widespread use [3]. Pharmacy records are less useful for drugs where the dose may vary. Patients may have accumulated some pills and this may have masked occasional nonadherence. However, we examined pharmacy records over a longer period to reduce the impact of this.

Studies of adherence to antiretrovirals are often cross-sectional, short-term or within research settings and have shown that adherence is an important predictor of successful suppression of viral load. Using the MEMS in a prospective study with a 6-month mean follow-up, Paterson [3] found that virological failure rates were lowest in those taking at least 95% of a regimen containing a protease inhibitor. This was confirmed by our examination of longer-term adherence (over 2 years) in unselected patients in an HIV clinic. A similar review of dispensing records in a centralized free pharmacy found that intermittent treatment (dispensing less than 12 months medication in a year) predicted increased mortality, but this study did not attempt to distinguish between nonadherence and interrupted treatment [5]. A correlation has also been observed between self-reported nonadherence, suboptimal

plasma drug concentrations and virological failure in an Italian cohort followed for 96 weeks [6].

We found that once a day medication had higher levels of adherence as measured by pharmacy record. It is important to appreciate, however, that we looked at individual drugs separately, and not at the whole regime. At the time of this study, few patients were taking mediation that could be taken once a day and at the same time of the day. However, our finding suggests that medication that can be taken only once a day is associated with higher levels of adherence, even if this is not necessarily what the patients feel will be the easiest to take [7].

Our study excluded 128 patients who had gaps in their prescriptions of greater than 6 weeks. We were not able to determine the reason for these gaps, but if patients had had their medication stopped because of poor adherence then the overall estimate of adherence in our study will be artificially high.

HIV clinics need to aim for high levels of adherence, and the critical levels we found (97% by self-report) imply that patients reporting one missed dose per 33 doses need extra support. This approximates to missing one dose a month for once-daily dosing or two per month for twice-daily dosing. The finding that patients report higher levels of adherence than pharmacy records indicate explains, at least partly, our observation that some patients fail to suppress their viral load despite reporting 100% adherence. Pre-existing resistance and inadequate plasma concentrations of drug are also likely to contribute to this. Improvements in adherence over time as measured by both methods may reflect a response by patients both to our regular questionnaire and to an adherence-support programme running in the clinic. The questionnaire and programme may also have caused some patients to overestimate their adherence. Measurement of adherence and support to improve it should now become a routine part of HIV clinical care and are likely to be cheaper than changing or intensifying antiretroviral combinations.

Future research will help identify the critical levels of adherence for different antiretroviral classes and different clinical situations. For example, a person with a high pretreatment viral load on a combination including a nonnucleoside reverse transcriptase inhibitor may need to maintain higher levels of adherence than someone with a lower pretreatment viral load whose combination includes a protease inhibitor.

Acknowledgements

We are grateful to Jeanette Venkataya and Kerri Boyd from the HIV clinic and Chris Thomas and Andrew Weiss from the pharmacy for the data used in this project.

References

1 Panel on Clinical Practices for Treatment of HIV Infection. US Department of Health and Human Services–National Institute of Health. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. US Department of Health and Human Services–National Institute of Health, 2004. http://aidsinfo.nih.gov/guidelines/

2 Read T, Mijch A, Fairley CK. Adherence to antiretroviral therapy: are we doing enough? *Int Med J* 2003; **33**: 254–256.

3 Paterson DL, Swindells S, Mohr J *et al*. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000; **133**: 21–30.

4 Wilson KJ, Doxanakis A, Fairley CK. Predictors of non-adherence to antiretroviral therapy. *Sexual Health* 2004; **1**: 251–257.

5 Hogg RS, Heath K, Bangsberg D *et al*. Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. *AIDS* 2002; **16**: 1051–1058.

6 Trotta MP, Noto P, Antinori A. Patient-report, physician-estimate and drug plasma levels as measures for adherence to HAART in the AdICONA study. *International Congress of Drug Therapy in HIV*. Glasgow, UK, November 2002: 89.

7 Stone VE, Jordan J, Tolson J. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. *J Acquir Immune Defic Syndr* 2004; **36**: 808–816.