Lost to follow up – contributing factors and challenges in South African patients on antiretroviral therapy

M Maskew, P MacPhail, C Menezes, D Rubel

Background. Patients who do not return for follow-up at clinics providing comprehensive HIV/AIDS care require special attention. This is particularly true where resources are limited and clinic loads are high. Themba Lethu Clinic at Helen Joseph Hospital in Johannesburg is a facility supported by PEPFAR funding through Right to Care (Grant CA-574-A-00-02-00018); more than 800 HIV/AIDS patients are seen there each week. Data on a sample of patients who failed to return for follow-up were analysed to identify the causes and to plan strategies to overcome the problem.

Methods. A group of 182 patients who missed follow-up appointments at the clinic were identified. Their files were examined to identify possible contributing factors. The patients were then contacted telephonically and asked their reasons for non-attendance.

Results. Results show that the leading cause of failure to follow up was financial (34% of patients). Patients cited transport costs and having to pay to open a file at each visit as the biggest monetary obstacles to obtaining treatment. Fifty-five per cent of patients lost to follow-up showed an improvement in CD4 count on treatment. Death accounted for 27% of the patients lost to follow-up and the mean (± standard deviation (SD)) duration of treatment in this group was only 8 (± 6) weeks. Of the patients in this group who had been seen at 4 months, 60% had failed to respond to treatment. The mean duration of ARV treatment before being lost to follow-up was 21 (± 28) weeks. The mean CD4+ count was 92 (± 74.5) cells/µl and the mean number of visits was 3.33 (± 2.17). Seventy-four per cent of the patients were on regimen 1A, and only 1 cited side-effects of medication as a reason for not returning.

Conclusions. This study highlighted financial difficulty as the major obstacle to obtaining treatment. There is evidence in support of providing ARV treatment free of charge to HIV-positive patients who qualify, as occurs in other provinces in South Africa. It is also suggested that providing ARV therapy at more local clinics in the community would make treatment more accessible. Provision of several months' supply of medicines per visit would help to reduce transport costs and minimise patient expenditure. These interventions may reduce the incidence of patients lost to follow-up in this community.

S Afr Med J 2007; 97: 853-857.

South Africa has one of the fastest-growing HIV-infected populations in the world. While the rollout of antiretroviral (ARV) therapy has brought much excitement and hope to both patients and practitioners, it has also brought many new questions and challenges. Adherence and regular clinic attendance are two of these challenges. This study attempted to trace patients at Themba Lethu Clinic, Helen Joseph Hospital, Johannesburg, who had been lost to follow-up, and to explore the reasons for non-attendance. Lost-to-follow-up patients were defined as those who had missed a clinic visit and who had not presented to the clinic within 1 month of the missed date. Adherence was defined as the correct and timely dosing of prescribed medications. The literature reviewed does not differentiate between the two definitions as patients in those studies were traced via pharmacy records – those who did not collect pharmacy prescriptions were assumed to be both non-adherent and lost to follow-up.

While adherence has always been viewed as a very important principle, it may be more critical than previously thought. Wood et al.[1] evaluated the effect of baseline CD4+ count and adherence on survival rates in an attempt to determine when to initiate highly active antiretroviral therapy (HAART). They found an increase in mortality when initiating at CD4 counts less than 200 cells/µl, but more importantly provided evidence that adherence was a statistically significant determinant of outcome at all CD4+ strata.

One of the more concerning outcomes related to poor adherence is the development of drug-resistant viral strains. Sethi et al.[2] sought to define the level of adherence associated with the greatest risk of resistance. The conclusion was that the greatest risk of clinically significant viral resistance occurs after missing 11 - 30% of ARV doses. No resistance was noted in patients with a cumulative adherence of less than 60%. That paper[2] emphasised that poor adherence is associated with viral failure, but not necessarily resistance. The greatest risk of resistance was with the reasonably adherent patient.

Many theories have been postulated regarding the main causes of non-adherence and various studies in different

Clinical HIV Research Unit, Department of Medicine, University of the Witwatersrand

M Maskew, MB BCh
P MacPhail, PhD, FCP, FRCP
C Menezes, MD, FCP
D Rubel, MB BCh, Dip HIV Man

Corresponding author: M Maskew (mhairi.maskew@righttocare.org)

853

communities have found a multitude of reasons. Many ARV regimens are complicated and have a high pill burden. There are multiple adverse side-effects associated with the drugs as well as interactions with other chronic medications. This may make compliance difficult for patients and may result in viral failure, development of drug resistance and limited future treatment options.

Trotta et al.[3] investigated which regimens were associated with the poorest rates of adherence and found that protease inhibitor (PI)-treated patients were the poorest adherers, while non-nucleoside reserve transcriptase inhibitors (NNRTI)-treated patients, especially those on efavirenz, were most adherent. Vomiting and sexual dysfunction while on PIs were identified as the main reasons for non-adherence.

Schiller[4] also studied the effect of adverse drug effects and compliance and found that 50% of patients in the study experienced adverse drug effects and it was the most common reason given for non-adherence in those patients. Most organ systems can be affected, depending on the drug or class of drugs being used; proper identification of adverse effects can therefore be difficult. The most common adverse effects suffered include gastrointestinal, neurological, metabolic, and cardiovascular events, although renal, dermatological, and haematological events may also occur.

While nausea, vomiting and anorexia appear to be the most common side-effects reported, diarrhoea was found to be a negative predictor of survival in HIV-positive individuals as it was associated with poor quality of life and poor adherence to treatment.

Adverse-effect management has included treatment interruptions and therapeutic drug monitoring, but it most commonly involves switching to another drug or class of drugs. This requires a complete understanding of HAART regimens and their associated complications. Schiller[4] found that HIV clinics employing clinical pharmacists were able to prevent adverse effects by suggesting alternative treatments, and by introducing medication counselling and compliance education.

Lignani et al.[5] concurred with these findings. They concluded that the main cause of treatment failure was medication side-effects. Education level and age were also identified as important predictors of compliance with ARV therapy.

However, a study done in Brazil by Monreal et al.[6] found adverse effects to be only the third most important reason for non-compliance. Forgetfulness was the most common reason given by patients, followed by running out of medication. Other predictors of poor compliance identified were complexity of dosing regimens and pill fatigue.

A Canadian study by Veinot et al.[7] found that youth (aged 18 to 25 years) were particularly prone to poor compliance.

Reasons included scepticism about the efficacy of medication, costs involved, stigma of disease and 'feeling different' as well as confusion about how to take the medication. The authors concluded that this age group may require developmentally appropriate, empowerment-based treatment approaches to help with treatment difficulties and adherence.

Another group prone to adherence problems are those with low literacy levels. Kalichman et al.[8] found that people living with HIV/AIDS who have lower health literacy show poorer treatment adherence and more adverse health outcomes. The authors designed a two-session plus one booster session nurse-delivered HIV treatment adherence intervention. Results from a pilot test involving 30 HIV-positive men and women showed that the nurse-delivered programmes increased HIV/AIDS knowledge, intention to improve adherence, and self-motivation for adhering to medications. Participants also showed improvement in medication adherence, with reduction in number of missed pills and reduction in number of doses taken at the wrong time.

However, patients with good educational levels are not without adherence problems. Moyle[9] studied compliance in an Edinburgh-based population and found that while higher educational level was associated with better adherence, such patients still had difficulty with work-time dosing as well as with depression and negative thoughts about treatment. It was found that patient knowledge of improved CD4+ count and viral load results had a positive impact on adherence.

In conclusion, factors associated with poor adherence have no social or cultural borders, and this should be kept in mind when attempting to find solutions to adherence problems. Patient counselling on correct dosing and motivation through periods of 'pill fatigue' are vital. There is good evidence for simplifying regimens. Any intervention must be appropriate to the social and cultural norms of the target population and must cater for differing literacy and educational levels.

Materials and methods

We identified a group of 182 patients who missed follow-up appointments at the clinic, and over a period of 2 months we examined their files for information such as gender, age, number of visits, most recent CD4+ count and viral load, ARV regimen and whether or not they were receiving a disability grant. We developed an interview questionnaire designed for telephonic use. The patients were was then contacted telephonically and asked their reasons for not attending their scheduled clinic visit, and also if they would consider returning to the clinic to attempt to resolve any problems identified. No controls were used.

Data were entered into a spreadsheet and were analysed using Microsoft Excel and SAS statistical software.

854

Results

Of the total number of clinic attendees (*N* = 5 849), 182 were recorded as having missed a clinic visit. We excluded 28 of these from statistical analysis as duplicate files were discovered for these people, i.e. the patients were not actually lost to follow-up. The final population group therefore totalled 154 (89 females and 65 males).

Of these, a further 84 patients had either incorrect contact details or no contact details recorded in their files and were therefore uncontactable.

Seventy patients were contacted and gave reasons for their lack of follow-up. Fig. 1 is the pie chart representation of the reasons given. The most common reason was financial difficulty, followed closely by death of the patient. Of the 19 patients found to have died, only 4 had illnesses recorded at the last visit. Two had proven tuberculosis, 1 had cytomegalovirus (CMV) retinitis and 1 had hepatitis B. The mean (± standard deviation (SD)) duration of treatment in this group was only 8 (± 6) weeks, and of the patients in this group who were seen at 4 months, 60% had failed to respond to treatment.

Eleven per cent of patients said that their medication had been stopped by their attending doctor but none knew the reason for the interruption in treatment.

Other reasons given included change of residence, with patients now receiving treatment from another facility, commencement of medical aid and private treatment, social problems such as incarceration, and the decision to try traditional medicine. Only 1.4% (*N* = 1) complained of side-effects.

Data obtained from the files of the group without correct contact details were included in the rest of the statistical analysis as these patients were believed to be genuinely lost to follow-up.

ARV regimen

Fig. 2 shows the distribution of the ARV regimens used by the patients. The majority of patients (74%) were on regimen 1A (stavudine, lamivudine and efavirenz).

The mean number of weeks on treatment (± SD) was 21 (± 28) weeks, and the mean number of visits was 3. 33 (± 2.17) visits.

CD4 counts

The mean baseline CD4 count for all patients was 92 (± 74.5) while the last recorded CD4 count showed a mean of 199.9 (± 136.8). Note that we were only able to calculate this value for those patients who had attended more than 1 clinic visit (*N* = 83).

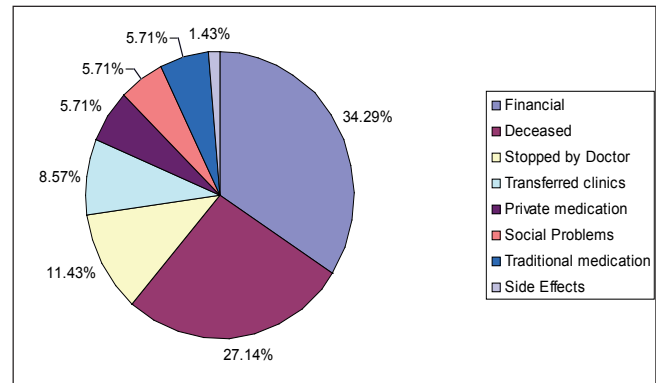We then calculated the mean CD4 baseline, the mean last
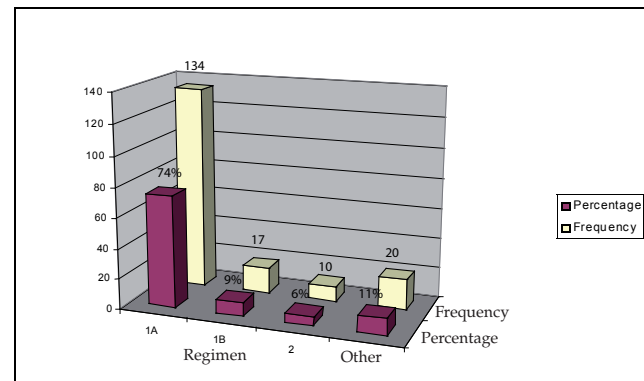

Fig. 1. Reasons given for loss to follow-up.

Fig. 2. Distribution of ARV regimens.

recorded CD4 level and the mean response to treatment (increase in CD4 count since initiation of treatment) for 2 groups, viz. the deceased patients (*N* = 19) and the patients who were still alive (*N* = 133). Two patients did not have recorded CD4 counts. Table I shows the comparative results. There seemed to be a trend in the results suggesting lower baseline CD4 counts in the deceased patients and also less of an increase in CD4 count on treatment for those who were deceased. A *t*-test done on these results showed no statistical significance; however a larger sample size may have shown the trend to be significant.

Age

The mean age of the study group was 35.3 (± 7.8) years for females and 38.4 (± 6.8) years for males. This correlated with the mean ages in the general clinic population.

Gender

We then compared the CD4 count variables (CD4 baseline, last recorded CD4 count and CD4 count response) across genders. This time there were statistically significant differences. The female patients had higher mean baseline CD4 counts and showed better CD4 responses once initiated on treatment than their male counterparts. The females had also been on

855

treatment for longer and had a higher mean number of visits. These results are summarised in Table II.

While fewer in number than females overall in this study, the males showed an increased representation in the study (42%) compared with the overall proportion in the clinic (30%). A chi-squared test showed this comparison to be statistically significant ($x^2 = 7.15$, $p = 0.01 < 0.005$).

Limitations

The lack of contact details in the files of some of the study group limited the study considerably. The study may also have been limited by the fact that all interviews were done telephonically and the location of the patient during the interview may have precluded them from speaking freely.

Discussion

One of the most significant results of this study was the staggering number of patients who could not be contacted because of lost files, incorrect contact details in files or no contact details recorded at all. Files that were available often had information missing, even information crucial to the patients' follow-up such as baseline CD4 counts and date initiated on therapy. This problem involved a number of factors. At the time of the study the clinic was largely reliant on paper files to keep patient details and records. Such files are easily lost when patients visit other clinics or get prescriptions filled. Duplicate files are made, but often information such as contact details, past visits and blood results are not recorded in those new files. The other factor to be considered is the level of mobility of this population sample. Most patients give only a cell phone number as a contact as they do not have a permanent residential address. Many frequently move around in search of work or on contract work. Additionally, often an entire family shares one cellphone and it is difficult to contact a specific member, especially with confidential or sensitive information. Many people change their cell numbers frequently because of theft or expiration of the sim card airtime window (usually 12 months).

The financial difficulties experienced by the population group in this study were clear, as financial difficulty was the most commonly cited reason for not returning for clinic visits. Patients at the clinic have to pay a fee every time they open their file to visit the doctor. Additionally, many patients travel long distances to get to the clinic as ARVs are not available at their local clinics, and transport costs are high.

For some patients, fear of disclosing their HIV status, especially to employers or colleagues, led to difficulty in obtaining and using treatment correctly. Patients feared dismissal if employers found out that were using ARVs and battled to hide their bottles of pills at work. Kaletra was particularly problematic as it must be kept refrigerated, which was impossible for those whose workplaces had no refrigerator

Table I. Comparative CD4 counts (deceased v. alive)

Variable	Alive	N	Mean	SD	SEM	Minimum	Maximum
CD4 baseline	No	19	61.526	65.962	15.133	2	196
CD4 baseline	Yes	133	97.752	81.201	7.041	1	533
CD4 last	No	8	151.88	138.9	49.11	12	446
CD4 last	Yes	75	204.88	135.62	15.66	4	544
CD4 response	No	8	2.4211	68.749	15.772	−95	250
CD4 response	Yes	75	17.519	133.79	11.515	−276	340

SD = standard deviation; SEM = standard error of the mean.

Table II. CD4 counts according to gender

Variable	Sex	N	Mean	SD	SEM	Minimum	Maximum
CD4 baseline	F	89	100.41	80.127	8.5416	1	533
CD4 baseline	M	63	84.048	80.235	10.109	2	462
CD4 last	F	51	228.24	144.55	20.443	4	544
CD4 last	M	32	157.44	112.14	19.825	10	474
CD4 response	F	51	29.273	134.96	14.386	−210	340
CD4 response	M	32	−3.954	115.63	14.342	−276	291
Visits	F	89	3.5955	2.1305	0.2258	1	10
Visits	M	65	2.9844	2.2002	0.275	1	11
Weeks on ARVs	F	89	23.9	31.3	3.3	0	242
Weeks on ARVs	M	65	17.7	23.1	2.9	0	114

SD = standard deviation; SEM = standard error of the mean; ARVs = antiretrovirals.

and very awkward for those who shared communal refrigerators. Timing of medication at work was problematic for patients who relied on public transport, as the unreliability of the latter meant they either got to work late to take their tablets or got home late for the evening dose. Even those patients who were open about their status with their employers felt that the clinic visits were too frequent (they must attend every month to collect medication even if they are not due for a doctor's visit) and long queues at clinics and the pharmacy meant missing an entire day's work.

Death of the patient was the second most frequent reason for loss to follow-up. However the results showed that there was a trend of low baseline CD4 counts and a poorer response to treatment suggesting that those patients who died on treatment sought help late and were already quite ill. Although we could not prove statistical significance, if the sample size was larger this apparent trend might have proved to be more significant.

The discrepancy in CD4 count between the genders was interesting as none of the literature reviewed showed any gender differences in ARV compliance. A much greater proportion of men were lost to follow-up than expected. Additionally, the female subjects demonstrated higher baseline CD4 counts and better CD4 responses while on treatment. The mean number of weeks on treatment was also greater in females. These findings suggest differences in attitudes to health and help-seeking behaviour between the genders, with women seeking help earlier and showing better compliance on treatment than their male counterparts. This may be related simply to male reluctance to seek help, or there may be a more socially rooted cause. The men in this study were more likely to be employed than the women, and taking a full day's leave every month consecutively for several months may have put their jobs at risk. For the contract or casual worker, the situation may have been even more difficult as missing a day's work would mean losing out on wages for the time missed or even loss of a contract completely.

Age was not found to be a significant predictor of clinic attendance.

The results of this study did not correlate with the findings of the reviewed literature concerning drug side-effects. Only 1 patient stopped his ARVs because of problems with side-effects. He developed hepatotoxity while on nevirapine and discontinued treatment after a hospital admission. The reason for this discrepancy may be that the population group in this study was more stoic in character than other study groups, or it may be that their financial worries dwarfed other problems that they were experiencing. None complained that the dosing regimen was too complex.

Conclusion

Strategies to improve adherence in this group must take into account the financial stresses of this population, particularly the male population. Strategies may include making ARV therapy free of charge and extending the rollout of ARVs to more local clinics. In this way patients could access their medication closer to their homes, reducing transport costs and reducing the number of clinic visits. Until this rollout happens, dispensing several months' worth of medication between doctors' visits would also mean fewer trips to the clinic. However these initiatives could only be considered for the well patient who does not require frequent medical check-up, and each patient's circumstances would have to be assessed individually.

In conclusion, it must be emphasised that differences in social status should be taken into consideration when initiating patients on ARV therapy. Each population has its own difficulties and attitudes towards treatment and these must be weighed carefully when considering strategies to ensure adherence.

References

1. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Antiretroviral treatment – when to initiate therapy: CD4+ cell count of 200. *Ann Intern Med* 2003; 139: 810-816.
2. Sethi AJ. Adherence and HIV drug resistance. *HIV Clin Trials* 2004; 5: 112-115.
3. Trotta MP, Ammassari A, Cozzi-Lepri A, *et al*. Adherence to highly active antiretroviral therapy is better in patients receiving non-nucleoside reverse transcriptase inhibitor-containing regimens than in those receiving protease inhibitor-containing regimens. *AIDS* 2003; 17: 1099-1102.
4. Schiller DS. Identification, management, and prevention of adverse effects associated with highly active antiretroviral therapy. *Am J Health Syst Pharm* 2004;
5. Lignani L, Greco DB, Carneiro M. Assessment of the compliance to antiretroviral drugs among HIV/AIDS patients. *Rev Saude Publica* 2001; 35: 495-501.
6. Monreal MT, da Cunha RV, Trinca LA. Compliance to antiretroviral medication as reported by AIDS patients assisted at the University Hospital of the Federal University of Mato Grosso do Sul. *Braz J Infect Dis* 2002; 6(1): 8-14.
7. Veinot TC, Flicker SE, Skinner HA, *et al*. 'Supposed to make you better but it doesn't really': HIV-positive youths' perceptions of HIV treatment. *J Adolesc Health* 2006; 38: 261-267.
8. Kalichman SC, Cherry J, Cain D. Nurse-delivered antiretroviral treatment adherence intervention for people with low literacy skills and living with HIV/AIDS. *J Assoc Nurses AIDS Care* 2005; 16: 3-15.
9. Moyle GJ. Practical issues: resistance & salvage, new antivirals and adherence. *AIDS* 1998; 12: Suppl 4, S18.

857