Personal barriers to antiretroviral therapy adherence: case studies from a rural Uganda prospective clinical cohort

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Abstract

Background: Although good adherence to antiretroviral therapy (ART) is essential for successful treatment outcomes, some patients may have specific personal barriers to ART adherence.

Objectives: To study specific personal barriers to ART adherence.

Methods: Quantitative data on patients' health status, ART adherence, CD4 cell counts and viral loads were collected, and qualitative data on life experiences of five patients with poor ART outcomes and adherence were also collected.

Results: Out of 35 patients with poor immunological and virological ART outcomes, 17 (49%) also had poor ART adherence. Patient 1 had no living child and did not disclose her HIV serostatus to her spouse because she wanted to have a child. Patient 2 was an orphan with neither social nor family support. Patient 3 stopped ART when she conceived, returned to the study clinic when pregnant again and was sickly. She was switched to second-line ART with satisfactory outcomes. Patient 4, a 14 year old orphan had missed ART for 2 months when his treatment supporter was away. Patient 5 aged 66 years stopped ART which he blamed for his erectile dysfunction.

Conclusions: ART adherence counselling should target specific personal barriers to ART adherence like: lack of family support, health and sexual life concerns, desire to have children and family instability.

Key words: Personal barriers, ART adherence, stigma, disclosure, children desire, sexual dysfunction

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Introduction

Since the universal rollout of antiretroviral therapy (ART), the natural history of HIV infection has changed from a fatal disease to a chronic manageable condition[1]. By the end of 2010, out of an estimated 10.4 million people who were eligible for ART in sub-Saharan Africa, 5.064 million (49%) were receiving it. This was an increase from the 3.911 (41%) million who were receiving ART out of the 9.6 million people who were eligible for ART by the end of 2009[2]. In Uganda, by the end of 2010 out of the estimated 577,000 who were eligible for ART, about 290,563 (50%) people were receiving it[3]. Antiretroviral therapy reduces viral replication in peripheral blood[4-6] and has improved the quality of life of HIV infected individuals through reduced morbidity and mortality[7-9].

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To achieve successful treatment outcomes, good ART adherence is vital although some individuals may not achieve good adherence to ART leading to poor viral suppression[10-11].

Before the Universal roll out of free ART in Uganda, lack of money to buy drugs was a major predictor of poor ART adherence[12]. Structural barriers; that is economic, institutional, political and cultural factors that hinder good ART adherence have recently begun to receive attention[13]. A systematic review identified fear of disclosure, forgetfulness, lack of understanding of treatment benefits and leaving behind medications, to be common barriers to ART adherence in developed and developing countries, while problems of access, including financial constraints and disruption in drug supplies were specific to developing countries[14].

Failure to disclose HIV serostatus, poor social and family support, concurrent use of other medications with ART have also been found to be associated with poor ART adherence[14-18]. Adolescents have been found to be less adherent to ART than adults and younger children, while orphanhood and lack of social support have also been reported to be associated with poor ART adherence

[15, 19-21]. Standardised approaches are often used to enhance improvement in adherence to ART, however this may not be appropriate in all cases as this paper illustrates.

In this paper, we used quantitative and qualitative methods to describe patients' specific personal barriers to ART adherence, health status, CD4 cell counts and viral loads ART outcomes. Life experiences of five patients with poor ART adherence who were purposely selected by the study counsellor and nurse to illustrate different age, gender and personal circumstances are described.

Methods

Study design, Setting and Patient's recruitment

These case studies are drawn from a population-based prospective open HIV-1 clinical cohort that was established in 1990, initially to study the natural history of adult HIV infection in rural southwest Uganda[2]. The study setting has a stable homogeneous population, with an adult HIV-1 prevalence that initially declined from 8.5% in 1990/1991 to 6.2% in 1999/2000, but then rose to 7.7% in 2004/2005[23-24]. Study patients are enrolled from a larger general population cohort that was established in 1989 to describe the population dynamics of HIV infection[25-26]. Free ART was introduced in January 2004 according to the Uganda National ART guidelines[27-28]. During the assessment for ART eligibility, patients were informed about ART eligibility criteria, life-long treatment, ART effects and side-effects, ART adherence, positive living including safe sex practices, nutrition and contraception. The importance of HIV serostatus disclosure, need for a treatment supporter and couple counselling were emphasised. Thereafter, a clinical evaluation, World Health Organisation (WHO) clinical staging[29] and a CD4 cell count measurement were done. Cotrimoxazole prophylaxis and other treatment were provided according to the National treatment guidelines[30]. Patients returned after about one week, when patients eligible to start ART were given an appointment for ART initiation and the rest were given a date for future reassessment.

ART Initiation

The first-line ART regimen consisted of two nucleoside and one non-nucleoside reverse transcriptase inhibitors, while the second-line ART regimen consisted of a triple therapy of tenofovir, emtricitabine (changed by the Ministry of Health to lamivudine in March 2010 due to cost and safety concerns) and ritonavir boosted lopinavir. Patients were reviewed routinely every three months, whenever they fell sick and monthly to renew their ART prescriptions. Adherence counselling was given before ART initiation and at ART prescription renewal visits. Study home-visitors visited patients who missed their ART renewal visits to remind them of their appointments. Patients identified with poor adherence received further intensified adherence counselling from the clinicians, a counsellor and a study nurse.

Measurement of outcomes

ART adherence measurements

At the patients' ART prescription renewal visits, the study nurse collected data on ART adherence using self report and pill count, but home visits for unannounced pill counts were not done. A patient was assessed whether he/she was late for the ART refill visit, and if yes, how many days he/she was late. The patient was asked for:

(a) the number of days he/she missed taking pills in the previous four days,

(b) whether he/she had missed taking ART pills the previous weekend,

(c) the last time he/she missed taking pills and

(d) the three most important reasons for forgetting to take the pills.

Thereafter, the study nurse counted the remaining pills and compared this with the expected pill balances. Poor ART adherence was defined as having missed one or more doses on 5% or more of the ART refill visits in the previous month.

CD4 cell counts measurements

We measured CD4 T-lymphocyte cell count at baseline and quarterly using the FACS Count method (Becton Dickinson, San Jose, CA, USA), with external quality control from the United Kingdom External Quality Assurance Scheme (UKNEQAS).

Viral loads measurements

Patients on ART had viral load measurements at baseline and every 6 months – from January 2004 we used the VERSANT RNA 3.0 (Bayer, Bayer HealthCare, NY, USA) assay (lower detection limit of 50 copies/ml) but due to problems with supply of reagents and lack of service support, this method was abandoned in September 2007. Between October 2007 and December 2010 we used the semi automated COBAS Amplicor MONITOR 1.5 (Roche, Roche Molecular Systems, NJ, USA) assay

(lower detection limit of 400 copies/ml). From January 2011 up to date we have used the fully automated COBAS AmpliPrep/TaqMan HIV Test (Roche Molecular Diagnostics (RMD), NJ, USA) (lower detection limit of 20 copies/ml), with external quality assurance from the Virology Quality Assurance Scheme (Rush University, Chicago, IL) and UKNEQAS. CD4 T-lymphocyte cell count measurements were done at the study clinic laboratory while plasma samples were stored in liquid Nitrogen at -80^{0}C within two hours of collection and later transported to the central laboratories in Entebbe for viral load measurements.

HIV drug resistance measurements

To identify drug resistance mutations in individuals with virological failure, sequencing was performed in the pol region using a Beckman Coulter automated CEQ 8000 capillary DNA Sequencer. Sequences were submitted to the University of Stanford HIV drug resistance database to identify the HIV-1 drug mutations associated with resistance.

Data collection and management

Selection of the case series

From 2004 to 2011, 379 patients were found to be eligible for ART, out of which 368 (97%) patients were started on ART. Patients with virological failure (defined as a viral load above 1,000 copies/ml) after 6 months on ART were identified, from which five patients with poor ART adherence were purposely selected by the study counsellor and nurse for qualitative interviews. During the 3 monthly routine visits, standardised questionnaires were used to collect quantitative data on the patients' medical and sexual history, ART adherence data and clinical examination findings. Laboratory data was also collected on standardised laboratory forms. Data were managed using an MS Access database. Qualitative data was collected by an experienced social science interviewer who visited each of the five patients in their homes and took a detailed life history account, including explaining their life experiences while on ART, and explored ART adherence and the associated barriers. Two such interviews were conducted in the local language (Luganda), at least 1 month apart and each lasting between 1-2 hours, they were then written up in English by the same interviewer.

Statistical methods

Data on the health status, ART adherence, CD4 cell counts and viral loads of five patients with poor ART adherence and outcomes was queried from the data base. The patients' clinical, haematological, immunological and virological characteristics at ART initiation and at the last clinic review were tabulated. Due to the small numbers, no statistical tests of comparisons were done.

Ethical considerations

The study was approved by the Science and Ethics committee of Uganda Virus Research Institute and by the Uganda National Council for Science and Technology. Informed consent/assent and confidentiality procedures were adhered to.

Results

Out of 35 patients with poor ART outcomes, 17 (49%) also had poor ART adherence with a median (interquartile range, IQR) CD4 cell count of 95 (63-156) cells/mm^3 and median viral load of 150,300 (85,000-240,000) copies/ml. Five patients with poor ART outcomes and adherence are described. Three were females, 2 (male and female) were teenagers and all had primary education level or lower as shown in table 1).

Patient 1 (Pt1)

Pt1 started ART in February 2004 when aged 29 years old as shown in table 2, she had poor adherence and she conceived twice with a detectable viral load; 106,000 copies/ml during the second pregnancy. In February 2009 during the second pregnancy, she was switched to second-line ART with good viral suppression after six months, but this rose to 416,000 viral copies/ml after another six months. She attributed her poor adherence to the headaches and diarrhoea she experienced while on second line ART and since she had no viral drug resistance, she was switched back to first line ART. However, her CD4 cell count continued to decline and the viral load rose. In February 2011, she was switched back to second line ART which was dispensed weekly to monitor side effects and adherence.

During the qualitative in-depth interview, Pt1 explained that she got married when aged 17 years but had five miscarriages and two infant deaths. She sorrowfully said: "……*Imagine that misfortune! I do not have a single child surviving! I would be having seven children with my late husband but I have zero!"* She added: *"….I anticipated that if I tried another man perhaps I would produce more children who would survive…"* Unfortunately the two babies she delivered with another man also

died though she reportedly gave nevirapine syrup to the last baby as instructed and weaned at six months after exclusive breastfeeding. On HIV serostatus disclosure, she said: *"Okay disclosing is not easy, for example with that second man, if I had disclosed he would have rejected me right away, then my trial for more children would be a failure!"*

Table 1: Patients' characteristics at initiation of antiretroviral therapy

Characteristics at ART initiation	Particular's for each patient				
	Pt1	**Pt2**	**Pt3**	**Pt4**	**Pt5**
Year of ART start	04/02/2004	06/08/2008	31/01/2007	08/07/2010	14/02/2005
Age (years)	29	41	17	14	66
Sex	Female	Female	Female	Male	Male
Education level attained	None	None	Completed primary	Still at school	Incomplete primary
Major occupation	Farmer	Farmer	Housewife	Student	Farmer
Religion	Catholic	Moslem	Moslem	Moslem	Catholic
Tribe	Nyarwanda	Ganda	Ganda	Ganda	Ganda
Tobacco use	None	None	None	None	Yes
Deliveries (females only)	2	2	0	Not applicable	Not applicable
Abortions (females only)	5	0	0	Not applicable	Not applicable
Living children	Not applicable	0	0	0	Not applicable

Table 2: Patients' clinical and laboratory characteristics at initiation of antiretroviral therapy and latest clinical review

Characteristics	Values for each patient				
	Pt1	**Pt2**	**Pt3**	**Pt4**	**Pt5**
At ART initiation					
Haemoglobin (g/dl)	12.7	12.6	11.0	12.1	12.8
WHO clinical stage	2	2	3	3	4§
Stating ART regimen[1]	AZT-3TC-NVP	AZT-3TC-NVP	AZT-3TC -NVP	AZT-3T C-NVP	AZT-3TC-EFZ
Weight (kilograms)	55	48	59	35	51
CD4 cell count (cells/μl)	154*	60*	100*	13*	392
Viral load (copies/ml)	274,348	48,900	386,306	311,000	33,964
At latest clinic review					
Time since ART start (months)	84	30	48	6	66
Current ART regimen[1]	TDF-3TC -LPV/r	AZT-3TC-NVP	TDF-3TC -LPV/r	AZT-3TC -NVP	None
Weight (kilograms)	51	44	67	42	54
Percent weight gain	-7%	-8%	+14%	+20%	+6%
CD4 cell count (cells/μl)	75	9	294	68	594
Viral load (copies/ml)	272,088	150,491	104	35,621	21,500

[1]ART regimens: AZT-3TC-NVP - zidovudine, lamivudine, nevirapine, AZT-3TC-EFZ - zidovudine, lamivudine, efavirenz; TDF-3TC-LPV/r - tenofovir, lamivudine, ritonavir boosted lopinavir
Main ART eligibility criteria: * CD4 cell count less than 200 cells/μl §WHO clinical stage 4

Patient 2 (Pt2)

Pt2 was eligible for ART in July 2007, but delayed ART initiation for almost a year due to lack of a treatment supporter, refusal to disclose her HIV serostatus and denial of HIV serostatus. She had poor ART adherence and in February 2011, her CD4 cell count had dropped to 9 cells/μl and the viral load was 150,491 copies/ml (table 2), when it was decided to dispense ART every two weeks to improve her adherence. During the in-depth interview, Pt2 reported that her mother died when she was 14 years old and she thereafter lived with several relatives. She got married and produced two children, but both died. She had been on ART for two years and although she denied ever missing taking ART, she admitted to ART fatigue: *"Feeling disgusted with taking it happens but then you say; if it is not because of this disease (AIDS) I would have abandoned taking it!"*

Patient 3 (Pt3)

In January 2007, Pt3 initiated ART when aged 17 years (table 2) but had poor adherence. She moved to the city and when she returned to her parents' home, she was pregnant, her CD4 cell count was 78 cells/μl and the viral load was 106,000 cells/ml. After intensified ART adherence counselling, she was switched to second-line ART and five months later her CD4 cell count was 319 cells/μl and viral load was less than 400 copies/ml. However, in August 2010 her viral load had risen to 15,700 copies/ml. It was decided to dispense ART every two weeks, and adherence improved but in February 2011 the viral load was 104 copies/ml in table 2). At in-depth interview, Pt3 reported that when she improved on ART, she had eloped with a man to the city but continued to come for her ART medications until when she conceived. She attended antenatal clinic in Kampala but never disclosed that she was on ART and she was instead put on antiretroviral medications to prevent mother to child transmission of HIV. She delivered in August 2008 but conceived again after seven months and returned to her parents' home while pregnant as her partner was also sick. This young woman struggled with her adolescent desire for sexual freedom (and children) and the constraints placed on her by her need for ART.

Patient 4 (Pt4)

In July 2010, Pt4 a 14 year old orphan was eligible for and initiated ART and cotrimoxazole prophylaxis, but after one month he defaulted for two months although ART was restarted thereafter. Six months after initiating ART his CD4 count was 68 cells/μl and viral load was 35,621 copies/ml (table 2). At in-depth interview, Pt4 said that he dropped out of school to attend to his then seriously sick late mother. After the mother's death, he became the head of household and did casual jobs for survival though he was sickly and weak. After the three months on ART, he said he was getting stronger and the skin rash had started drying up and had become less itchy. On taking ART, he said: *"Sometimes I can take the drugs without having eaten anything, then I feel sleepy and dizzy. Anyway there were some days when my uncle (his treatment supporter) had a sick child who was admitted. Within those days (actually two months), I did not take the drugs because there was no one to give it to me"*. He resumed ART when the uncle returned and he was eventually allowed to keep his own medicines. However, his adherence remained poor and in October 2011 his CD4 count was 28 cells/ μl and he also had a urethral discharge that grew *Neisseria gonorrhoeae* on culture.

Patient 5 (Pt5)

Pt5 then aged 66 years initiated ART in February 2005 (table 2) but stopped taking it in August 2008. At in-depth interview, Pt5 who was married explained that he trusted and used herbal medications that he said restored his manhood and although he was not sexually active, having an erection indicated that he was still a full man. He said western medicines were causing him erection problems. He said: *"I got the same experience when I started receiving the medicine (ART) from your clinic so I decided to do away with the kizungu (Western) medicine! The normal status of my 'man' (erection) is what gives me hope that I am still healthy although I no longer have sexual intercourse. When you no longer have an erection, you ask yourself; of what importance am I among people now?"*

Discussion

In the clinical cohort where these five patients received HIV care, about a half of patients with poor ART outcomes also had poor ART adherence. We identified specific personal reasons why this was so, which provided the themes we used in our analysis. The themes were: failure to disclose HIV serostatus driven by the desire to have children, orphan-hood and lack of family support, adolescence, family instability and sexual desires. Strengths of this study are the long prospective nature of the clinical cohort, the use of both quantitative and qualitative study methods to understand their

specific personal barriers to ART adherence. However, the small number of patients with both poor treatment outcomes and adherence data and the fact that life histories interviews were conducted for only five patients hinders making inferences to the general population or other similar studies conducted elsewhere. Bias might have been introduced into the study by the same interviewer conducting the life history interviews in Luganda, translating and writing them up in English.

HIV infected individuals whose health has been restored by ART often wish for a partner and desire for children[31-35] as they are reinstated into a social world that places a value on marriage and child-bearing. Among the many drivers for new relationships among people on ART is the desire for sex and children[36-37]. All the children from Pt1's first marriage had died, yet death of children and dissolution of previous marriages are some of the factors associated with a desire for children among individuals on ART[31]. However we did not find any other study that has reported the association between the desire to have children and ART adherence. Pt1's desire to have children hindered her disclosure of her HIV serostatus to the partner, and most probably she could not take her pills daily when the partner was present, yet failure to disclose HIV serostatus is a barrier to ART adherence[14]. Pt2's poor ART adherence was due to poor social and family support, and also reluctance to disclose her HIV serostatus, these factors have previously been found to be associated with poor ART adherence[14-16].

HIV infected adolescents face adherence challenges during their transition to adulthood like palatability issues, pill burden, interference of ART with lifestyles, adolescent HIV infected patients' growing independence, increased peer pressure, fear of stigmatization and other factors[38-41]. Pt3 was an adolescent who dropped out of school and eloped with a man, in South Africa, adolescents were less adherent to ART than adults[19], while in the USA, adolescents (13-18 year old) were less likely to achieve undetectable viral loads than children less than 13 year old[20], and in Haiti where HIV-infected youths and adolescents had poor ART adherence[21]. Pt4 was also an adolescent who had sexuality challenges, and the *N. gonorrhoeae* urethritis was proof of unprotected sexual intercourse. Pt4 was an orphan who had lost his mother yet ART adherence problems among adolescents are aggravated by orphan-hood and lack of social support[15, 19]. In Uganda, patient-selected treatment supporters improved ART treatment outcomes, especially at the start of ART[42-43]. Pt2 had no treatment supporter which hindered her ART adherence while the treatment supporter of Pt4 did not leave the ART medications to him or with another adult to supervise the intake. There is need to inform treatment supporters on what to do under such circumstances, however, given that Pt4 did not inform anyone else of his problem, he may have used his Uncle's absence as an excuse to avoid taking his medication.

Pt5 was an older man, care for older HIV-infected patients has challenges yet the proportion of HIV infected patients aged 50 year and above has increased mainly due to better survival (due to ART) and increased incidence among this age group[44]. The age of HIV infected patients both at diagnosis and those in care is also increasing all over the world, mainly due to diagnostic delay and late presentation [45-46]. As a consequence, older HIV infected patients are diagnosed at lower CD4 cell counts, and frequently have co-morbidities (due to HIV and the ageing process) and are on co-medications that can affect the efficacy and safety of ART[45, 47]. Despite having similar virological response to ART like the younger patients, older patients usually have poorer clinical and immunological response[44-46, 48]. Pt5 attributed his erectile dysfunction to ART, and although age and a protease inhibitor based ART regimen were independently associated with erectile dysfunction[49], he was not on a protease inhibitor ART regimen. He said that the herbal medications improved his erectile function, but natural aphrodisiacs have not been found to be an effective treatment for male or female sexual dysfunctions[50]. In Uganda, use of traditional herbal medications is common and in one study 33.7% of patients on ART were also reported to be using herbal medications. However, in that study most of the patients used herbal medications for HIV associated symptoms and not to improve sexual performance [51]. Concurrent use of herbal treatment was associated with ART non-adherence, though their use significantly declined after six months on ART[18] Similar declines in herbal remedies use after ART initiation have been reported in Uganda[17] and in South Africa[52].

Conclusion

Although it is difficult to precisely predict which patient will eventually have poor ART adherence, during ART eligibility assessment visits, a qualitative

research approach and careful counselling according to individual medical, social and mental status is required in order to understand the different reasons for poor adherence.

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