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Adherence and Treatment Change among HIV/AIDS Patients in Ghana – A Nested Case Control Study

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Abstract

Objective: A level of 95% adherence to antiretroviral therapy (ART) has been found to benefit HIV/AIDS patients. Low adherence may lead to treatment failure, and may subsequently result in treatment change. The main objective of this study was to evaluate the effect of ART adherence on treatment change

Methods: Data were extracted from available written clinical and pharmacy records, and the electronic database at the Korle-Bu Teaching Hospital. Cases comprised all those (≥15 years) who experienced a first treatment change after starting first-line ART between 1/1/2004 and 31/12/2009. Controls (who did not change treatment) were sampled from the same cohort of ART starters and matched to cases on date ART was started. Adherence was determined using the proportion of days covered (PDC) approach and poor adherence was defined as PDC levels below 95%. Measures of effect were calculated using conditional logistic regression.

Results: The 298 cases and 298 matched controls were similar in most baseline characteristics. Among cases 20.1% (60/298) switched to second-line therapy and the rest had treatment substitutions. Overall, 88.9% of controls compared with 79.9% of cases had adherence levels greater than or equal to 95% (p=0.003). After adjusting for possible confounders, an adherence level below 95% was associated with almost four times (ORadj=3.56 (95% CI 1.60 to 7.88)) the likelihood of having a treatment change.

Conclusion: This study showed that insufficient ART adherence was associated with about four times the likelihood of treatment change. Policy makers must partner researchers to engage patients more often, to unravel the causes of non-adherence, and make the necessary interventions for patients to achieve maximum benefits from dispensed medicines.

Keywords: Adherence; Treatment change; HIV; AIDS; Ghana

Introduction

Public access to antiretroviral medicines in Ghana began in mid-May 2003. By the end of December 2012, a total of 73,339 clients were receiving antiretroviral therapy (ART) [1] throughout the country. The availability of ART has led to improved quality of life and an increase in life expectancy among HIV/AIDS patients successfully treated [2]. This is primarily due to the achievement of low viral loads and improved CD4 cell counts [3] as a result of optimal adherence [4,5].

For ART programs to succeed a policy document on treatment guidelines should be available. The first treatment guideline for ARTs in Ghana was published in 2002. By the end of 2009 there have been two revisions of the document, the first in 2005 and again in 2008 [6]) with each incorporating the most recent evidence. Presently, ART adopted for use in Ghana include only first and second line medicines. First line medicines include a combination of nucleoside reverse transcriptase inhibitors (NRTI) and a non-nucleoside reverse transcriptase inhibitor (NNRTI), and second line treatments comprise a combination of NRTI and a protease inhibitor. All patients (with the exception of those with HIV-2) begin treatment with a first line option.

Researchers have found that adherence plays a crucial role in viral suppression of HIV replication [7-9]. Other researchers have linked poor adherence to drug resistance [10,11]. Paterson et al. [12] and Low-Beer et al. [13] have shown that among HIV/AIDS patients who administered at least 95% of their medication, 78%-84% showed undetectable viral load compared to 45%-64% among those who took between 90%-95% of their medication. In a sub-study of a multicentre, randomized, open-label, comparison-controlled trial, Ickovics et al. [14] reported that HIV/AIDS patients whose degree of adherence was less than 95% were 3-5 times more likely to have treatment failure compared to those with adherence levels of 95% or higher. Furthermore, it has been found that low adherence is a major predictor of treatment failure [15] which may lead to changing from one group of medication to another. In resource limited settings adherence is determined most of the time from patient self-report or from pharmacy records [16] (where these exist and are up to date). In a study using pharmacy refill information it was shown that using adherence measurements to predict treatment failure were as accurate as CD4 cell counts [17].

If treatment outcomes are not as expected, a treatment change is the most possible alternative. In a study in West-Africa on reasons for

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treatment change to second line therapy, Landier et al. [18] noted that ART modification could involve a replacement of one or more drugs in a combination or a change involving the introduction of a new drug class. Treatment modification could be as a result of a number of reasons. These include the possibility of an adverse drug reaction [19], a treatment failure, or due to ART policy changes as a result of new research findings. As ART is scaled up, chances are that more people will have their treatment changed to a second-line therapy. The cost of second line therapy is about six to ten times higher than first-line treatment [20]. Hence, there is the need to monitor those on first-line medications in order to prevent any unnecessary switches.

Many HIV studies [21,22] so far have looked at treatment failure and discontinuation of ART from the perspective of temporal trends or taxonomy of possible determinants. The present study aims to elucidate a possible association between insufficient adherence to ART and treatment change among HIV/AIDS patients at the Korle-Bu Teaching Hospital in Ghana.

Methods

Study setting

The Fevers Unit of the Department of Medicine and Therapeutics of the (KBTH) was the study site. The Unit is responsible for the registration and management of all patients diagnosed with HIV in the KBTH as well as those referred from other health institutions in Ghana. Provision of antiretroviral therapy in the Unit started in December 2003. As of December, 2009 about 4850 clients have been initiated antiretroviral treatment at the Fevers Unit with about 3,740 of them still on treatment. There are three major out-patient clinic days per week, each with an average clinic attendance of about 120 patients.

Study eligibility

Patients, who started treatment between 1st January, 2004 and 31st December, 2009 were eligible for the study if they started treatment at least one month before the end of the study period. Only those 15 years or older, enrolled at the Fevers Unit of the KBTH, and received ART at the Pharmacy Department of the KBTH were included in the study. Patients were included in the study if they were on triple therapy. Patients were excluded from the study if their clinical records and/or pharmacy records were not available. Patients who were transferred to other centers to continue treatment were also excluded because such patients went along with their medical records.

Study design

This was a nested case control study involving patients 15 years or older on antiretroviral therapy at the KBTH HIV treatment center. Cases were patients within the treatment cohort whose treatment were changed by an HIV clinician from the baseline (first-line) treatment to another first line treatment option (substitution) or from the baseline (first-line) treatment to a second-line treatment (switch). Changes in dose were not captured as treatment changes. The date of (first) change was the index date.

Controls were sampled from the same group of first-time ART users, at the time a case occurred, and matched on treatment initiation date plus or minus 15 days. The "Guidelines for Antiretroviral Therapy in Ghana" [6] was used as the reference for medicine classification as first or second line regimen.

Data collection and definitions

On every clinic visit day, patients are given a date for the next clinic appointment. At the pharmacy, medicines are dispensed to match the period until the next appointment date. For treatment naïve patients the first two treatments cover a period of fifteen days each. The third treatment is for one month, and depending on the patient's adherence record and availability of medicines, subsequent treatment may be up to four months. In this study patients who experienced a change in therapy were traced backwards to at most the thirteenth month before the date of change in both clinical and pharmacy records to ascertain attendance information. For those whose backward history was less than twelve months the whole period of treatment was used to establish attendance information. This was also done for corresponding controls. The appointment dates and the actual reporting dates in clinical records during this period were compared. Because cases were matched to controls on treatment initiation date, every risk pair had similar period of observation. In the case of pharmacy records, the appointed dates for refill and the actual reporting dates were compared. Using pharmacy records the number of default days for each patient (proportion of days covered (PDC) [23]) was determined and this was used as a surrogate measure for adherence. Those with a PDC of less than 95% were classified as non-adherent and those with a PDC of 95% or higher were classified as adherent to ART. Additionally, those with 100% adherence were identified.

Using a data extraction questionnaire, socio-demographic and clinical information on selected patients was gathered from clinical records as well as pharmacy records. Socio-demographic variables included sex, education at baseline, marital status at baseline and occupation at baseline. For occupation the covariate "others" were predominantly people who were still in school. Other variables were religious affiliation at baseline and age at onset of treatment. Mean difference in BMI of cases and controls was defined as the mean of the difference between BMI at the start of treatment and BMI at treatment change/end of observation period for cases and controls respectively. Clinical data were made up of baseline variables including presence of HIV/AIDS symptoms, CD4 count, WHO staging, source of funding health care and treatment type. Physician reported adverse events during follow-up post-treatment were also captured. Socio-demographic and clinical variables were extracted from the clinical records. Information on type of ART used, date of treatment initiation, date of refill and date of treatment change were obtained from pharmacy records. Data extraction was carried out by only the lead author to maintain uniformity.

Ethical clearance

Ethical approval for this study was obtained from the Ethical and Protocol Review Committee (EPRC) of the University of Ghana Medical School.

Statistical analysis

Univariate analysis included descriptive statistics of socio-demographic, clinical and treatment data. Mean differences in continuous variables and normal distributions were determined using the t-test and scatter diagrams respectively. Classical Mantel-Haenszel method was used to calculate crude odds ratios and other exploratory statistics. For multivariate analysis conditional logistic regression was used. The effects of possible confounders including age, sex, educational status, occupation, religion (i.e. socio-demographic variables) and baseline CD4 count, baseline WHO stage of disease, body mass index, source of funding, adverse drug event after treatment initiation (i.e. clinical variables) on the crude odds ratio were explored individually. Variables that shifted the crude odds ratio by at least 10% [24] higher

or lower were kept in the final model and their combined effect on the relationship between adherence and treatment change was ascertained. Likelihood ratio tests were done to ascertain effect modification, suspecting that at least sex will modify the effect of the results.

Results

There were 298 patients who had a treatment change (cases) and 298 matched patients who continued their initial ART medication (controls). The median age of cases was 42.7 years (inter-quartile range (IQR) 36-51 years), and for controls the median age was 42.7 (IQR 52-36). About 65% (195/298) of the cases were female. Among cases, 20.1% (60/298) changed treatment to a second line and the rest (79.9%) changed to another first line medicine.

Table 1 shows baseline socio-demographic variables for cases and controls, and the relationship between these variables and treatment change. It can be seen that most of the socio-demographic variables did not show any statistically significant difference between the two groups of patients.

Table 2 shows clinical or treatment parameters for both groups and data on possible determinants. At baseline the CD4 cell count ranged from 0 to 399 cells/mm^3 (mean=104.9 cells/mm^3) for cases and from 1 to 443 cells/mm^3 (mean=135.6 cells/mm^3) for controls. At exit the CD4 cell counts ranged from 1 to 1020 cell/mm^3 and from 2 to 1024 cells/mm^3 for cases and controls respectively. The highest CD4 cell count recorded in this study was 1401 cells/mm^3. The mean difference in BMI among cases was 1.63 (SD=3.04) and for controls it was 1.92 (SD=2.66) which was not statistically significant between both groups. Using 95% adherence as the cut-off, 84.4% of all patients in this study adhered to treatment. A total of 88.9% of all patients who did not change treatment adhered to treatment compared with 79.9% (p=0.003) of those who changed treatment (Figure 1). When adherence was categorized into three bands (100%, between 99.99% and 95%, and below 95% only 48.8% of all patients in the study recorded 100% adherence with antiretroviral therapy (p<0.0001). Exploring adherence levels further among those who changed treatment, it was found that 79.4% adhered to treatment among those whose medication was changed from one first line treatment to another first line compared with 83.3% (p=0.01) of those who changed from one first line to a second line treatment.

Cases had a higher risk of clinical symptoms at treatment initiation (OR=1.67, 95% CI 1.19 to 2.34), developed a physician reported adverse reaction (OR=48.33, 95% CI 15.41 to 151.62), more frequently had CD4 counts less than150 cells/mm^3 (OR=2.08, 95% CI 1.10 to 4.15) and had a higher risk of being diagnosed with a WHO stage IV at baseline (OR=1.44, 95% CI 1.02 to 2.03) compared to controls. Furthermore, cases` seemed to use a stavudine based treatment more frequently (OR=1.36, 95% CI 0.96 to 1.91) but this was not statistically significant.

Univariate analysis showed that low adherence rates were associated with an increased risk of treatment change (OR=2.35 95% CI 1.33 to 4.15, see Table 3). Only the presence of an adverse drug reaction and occupational status shifted the crude odds ratio by a margin greater than 10% upwards or downwards. Only these two variables were therefore maintained in the final model for multivariate analysis. After adjusting for these two possible confounders (Table 3), the odds ratio between insufficient adherence and treatment change was 3.56 (95% CI 1.60 to 7.88). Stratification by type of treatment change yielded similar results; those who did not adhere to treatment among those who changed treatment from one 1st line ART to another 1st line were 2.40 (95% CI 1.31 to 4.38) times as likely to do so and for those who changed from a 1st treatment to a 2nd line treatment option, the OR was 2.00 (95% CI 0.37 to 10.92). Likelihood ratio tests performed did not show any significance of effect modification among the variables.

Discussion

This study examined the association between adherence and treatment change using a matched case control approach among adult

Variable	Cases (%)	Controls (%)	p-value
Sex	**(N=298)**	**(N=298)**	
Male	103 (34.6)	106 (35.6)	Reference
Female	195 (65.4)	192 (64.4)	0.802
Age (years)	**(N=298)**	**(N=298)**	
30-39	94 (31.5)	89 (29.9)	Reference
15-29	19 (6.4)	22 (7.4)	0.617
40-49	100 (33.6)	95 (31.9)	0.500
50-59	58 (19.4)	68 (22.8)	0.113
≥60	27 (9.1)	24 (8.0)	0.655
Marital status	**(N=293)**	**(N=296)**	
Single	63 (21.5)	55 (18.6)	Reference
Married/cohabiting	159 (54.3)	160 (54.1)	0.492
Divorced/separated	40 (13.7)	47 (15.9)	0.020
Widow/widower	31 (10.6)	34 (11.5)	0.617
Educational status	**(N=288)**	**(N=295)**	
Basic and Senior High	219 (76.0)	229 (78.6)	Reference
No education	42(14.6)	41 (13.9)	0.814
Higher education	27 (9.4)	25 (8.5)	0.758
Occupation	**(N=284)**	**(N=294)**	
Self-employed	196 (69.0)	221 (75.2)	Reference
Unemployed	32 (11.3)	27 (9.2)	0.343
Professionals	34 (12.0)	30 (10.1)	0.238
Others	22 (7.7)	16 (5.4)	0.564
Religious affiliation	**(N=287)**	**(N=297)**	
Christian	235 (81.9)	257 (86.6)	Reference
Other religions	52 (18.1)	40 (13.4)	0.123
Source of funding	**(N=289)**	**(N=293)**	
Out of pocket	180 (62.3)	203 (69.3)	Reference
Some form of funding	109 (37.7)	90 (30.7)	0.090

Table 1: Socio-demographic characteristics of cases and controls.

Variable	Case (%)	Control (%)	Odds ratio (CI)	p-value
Initial BMI (kg/m^2)±	**(N=240)**	**(N=240)**		
20-24.99	91 (37.9)	98 (40.8)	Reference	
≥25	24 (10.0)	38 (15.8)	0.69 (0.30 to 1.62)	0.394
<20	125 (52.1)	104 (43.4)	1.18 (0.74 to 1.86)	0.486
Clinical symptoms$^{\alpha}$	**(N=294)**	**(N=298)**		
No	131 (44.6)	170 (57.0)	Reference	
Yes	163 (55.4)	128 (43.0)	1.67 (1.19 to 2.34)	0.003
Adverse drug reaction	**(N=289)**	**(N=287)**		
No	133 (45.6)	277 (95.8)	Reference	<0.001
Yes	159 (54.4)	12 (4.2)	48.33 (15.41 to 151.62)	
Initial CD4 cell count	**(N=293)**	**(N=295)**		
>250	20 (6.8)	36 (12.2)	Reference	
150-250	70 (23.9)	91 (30.8)	1.14 (0.41 to 3.15)	0.487
<150	203 (69.3)	168 (57.0)	2.08 (1.10 to 4.15)	0.019
Initial WHO staging	**(N=293)**	**(N=296)**		
I-III	229 (78.1)	251 (84.8)	Reference	
IV	64 (21.9)	45 (15.2)	1.44 (1.02 to 2.03)	0.038
Initial treatment	**(N=298)**	**(N=298)**		
AZT/3TC/EFV	85 (28.5)	70 (23.5)	Reference	
AZT/3TC/NVP	76 (25.5)	71 (23.8)	1.09 (0.70 to 1.71)	0.698
d4T/3TC/EFV	63 (21.1)	84 (28.2)	1.62 (1.03 to 2.55)	0.038
d4T/3TC/NVP	61 (20.5)	60 (20.1)	1.19 (0.73 to 1.94)	0.482
OTHERS	13 (4.4)	13 (4.4)	1.13 (0.51 to 2.79)	0.686
AZT or d4T combination	**(N=298)**	**(N=298)**		
AZT base	161 (54.0)	141 (47.4)	Reference	
d4T base	124 (41.6)	144 (48.3)	1.36 (0.96 to 1.91)	0.084
Other combinations	13 (4.4)	13 (4.4)	1.13 (0.50 to 2.53)	0.784

$^{\alpha}$Clinical symptoms at treatment initiation; ±Body mass index at baseline

Table 2: Clinical and treatment parameters of cases and controls and crude odds ratios of association.

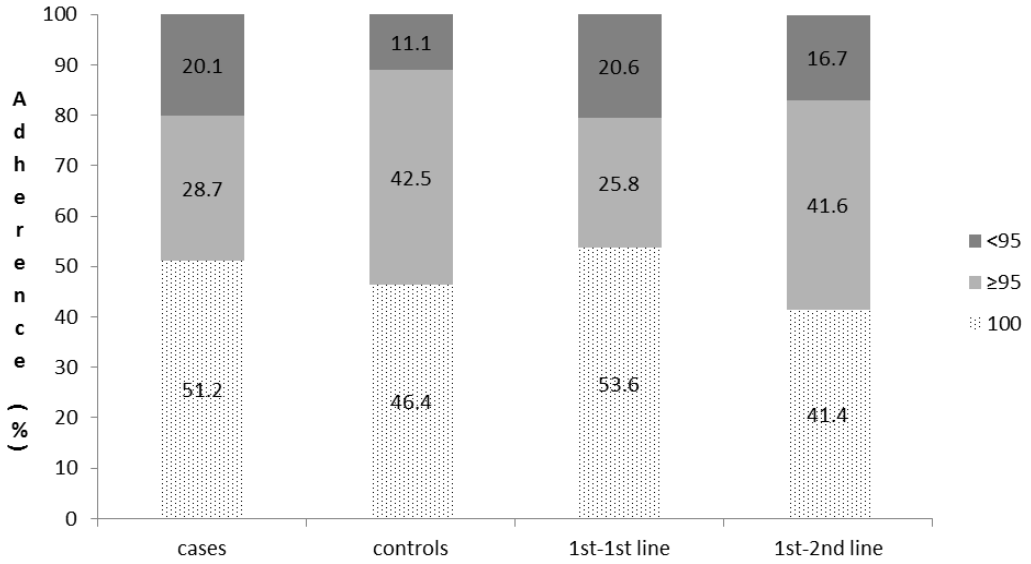

Figure 1: Adherence levels for cases and controls and for cases who changed treatment.

Adherence	Cases (%) (N=298)	Controls (%) (N=298)	Crude OR (95% CI)	Adjusted ORadj[1] (95% CI)	p-value
≥95%	238 (79.9)	265 (88.9)	Reference	Reference	
<95%	60 (20.1)	33 (11.1)	2.35 (1.33 to 4.15)	3.56 (1.60 to 7.88)	0.002
1st line to 1st line	**(N=238)**	**(N=238)**			
≥95%	189 (79.4)	213 (89.5)	Reference		
<95%	49 (20.6)	25 (10.5)	2.40 (1.31 to 4.15)		
1st line to 2nd line	**(N=60)**	**(N=60)**			
≥95%	50 (83.3)	51 (86.7)	Reference		
<95%	10 (16.7)	9 (13.3)	2.00 (0.37 to 10.92)		

Table 3: Univariate and multivariate analysis of the relationship between adherence and treatment change.

patients who initiated ART in Ghana. Adherence was determined using the PDC method and 95% coverage or higher was taken as being sufficiently adherent. Controls in this study were more adherent to treatment compared with cases.

Multivariate analysis results showed that non adherence is independently associated with almost four times the odds of treatment change. Kwobah et al. [21] identified that non adherence was associated with almost three times the odds of treatment failure and Gonzalez-Serna et al. [22] found that an adherence level greater than or equal to 95% independently reduced treatment discontinuation by 61%. Ickovics et al. [14] have reported that HIV/AIDS patients whose degree of adherence was less than 95% were 3-5 times more likely to have treatment failure compared to those with adherence levels of 95% or higher and treatment failure is one of the most common reasons to switch therapy [25]. Interestingly, non-adherence was similarly associated with a change to another first line or to a second line therapy, although the latter was not statistically significant due to low numbers.

Demographic variables in this study were not associated with a change of therapy. The result is not very different from the multi-cohort study of 17 ART programmes [26]. Most clinical and treatment parameters, however, were associated with treatment change. With decreasing CD4 cell count at ART initiation there was an increasing tendency for a treatment change. A number of researchers [27-29] have made similar observations. These findings call for treatment initiation to begin during early diagnosis of HIV infection (when CD4 cell counts are most likely to be higher). Also counseling and testing services need to be stepped up to identify patients during early stages. The development of physician reported adverse drug reaction to ART in this study was linked to treatment change. Furthermore, patients with adverse drug events seemed to have developed low adherence levels. This link may be confirmed with the help of predictive studies beyond this paper but calls for patients to be more informed on the benefit-risk profiles of their medicines.

It was found that overall more patients adhered to treatment compared to the study in Cote d'Ivoire [30] in which 74.3% of participants adhered to treatment using a 95% cut-off for adherence calculated over a four day period. In the Royal Free Clinic cohort in London [27] 45% of participants adhered to treatment using the proportion of days covered approach. However, adherence in our study was lower (93.4% kept appointments regularly) than that reported by Baqi et al [31]. It is important to maintain the high adherence levels observed and continue to strive harder because of the consequences of low adherence [32,33]. At the Korle-Bu Teaching Hospital HIV patients undergo three sessions of adherence counseling before treatment initiation. This is to ensure that they have a good knowledge of the disease and the rational for better treatment outcomes during long periods of therapy. It is important therefore, to try and identify those factors that lead to poor adherence in this setting and carefully monitor and evaluate them (in addition to other known factors) so they do not fall below the levels recommended by the WHO [34].

There were limitations in this study. It was assumed that once an antiretroviral medicine is prescribed and dispensed, it will be

administered but in reality it may be different. The best approach is to calculate actual doses administered, although this may be very difficult to achieve. But using the PDC [23] which is an objective measurement of adherence especially among chronic diseases [35], it is believed that errors will be minimal. Lack of a statistically significant association among the subgroup of those who switched to second line treatment could be as a result of reduced sample size leading to a wide confidence interval. In particular, odds ratios in matched case control studies are dependent only on the discordant pairs. For a reduced sample size, the discordant pairs are reduced accordingly leading to a lowered statistical power [36] to predict an outcome even though one may exist. A more powered study is therefore recommended in future.

Conclusion

Among HIV/AIDS patients, the main guarantee for improved life expectancy is an intervention with antiretroviral therapy. However, successful treatment outcomes depends on optimum adherence levels. This study identified that adherence to ART is linked to treatment change, and non-adherent patients have increased tendency of being affected. This could pose a problem to most low and medium income countries because of higher costs of alternative antiretroviral medicines. Policy makers must partner researchers to engage patients more often to unravel the causes of non-adherence, and make the necessary interventions for patients to achieve maximum benefits from dispensed medicines.

Competing Interests

None declared. This research was not sponsored.

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