High adherence to antiretroviral treatment despite frequent adverse effects among people living with HIV in Dodoma, Tanzania

Master thesis in Medicine

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1. Abstract

Master thesis, Programme in Medicine

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Background: To reach satisfying results from the antiretroviral treatment of HIV the adherence needs to be > 95 %. There are also problems with toxicity and side effects of the antiretrovirals that affects a lot of people worldwide**.** Following this, it is of great importance to investigate how well the antiretroviral therapy (ART) is working.

Objectives: To examine how the ART among HIV positive patients is functioning and also to investigate potential differences between men and women.

Methods: The cross-sectional study was done at a Care and Treatment Clinic in Dodoma, Tanzania. The 200 patients (79 men and 121 women) answered a self-administered questionnaire and information was collected from the medical records.

Results: The self-reported adherence level was 88% among the participants, 75% of the patients suffered from any adverse effect. The non-adherent patients had a tendency towards more adverse effects. The knowledge about HIV transmission was low regarding mother to child transmission (MTCT) and blood transfusion/needles as routes of transmission. Some differences between sexes were found; men had lower CD4 levels, lower level of knowledge about HIV and a tendency towards experiencing larger economic impact due to HIV.

Conclusions: The ART was functioning well in most aspects with a relatively high level of adherence, despite frequent adverse effects. Additional studies with a larger patient material are needed to further investigate differences between men and women for the outcome of therapy.

Keywords: HIV, antiretroviral therapy, adherence, adverse effect, knowledge

2. Introduction

2.1 Background

2.1.1 HIV globally

HIV is a major global challenge causing great health issues worldwide. As much as 78 million people have been infected of the virus since the beginning of the epidemic, and almost 39 million people have died of HIV (1). The worldwide prevalence of people living with HIV between 15-49 years is 0.8 % (1). However, there are big differences between regions and countries throughout the world. At the end of 2013, there were approximately 35 million people in the world living with HIV (2) and in the same year 1.5 million people died of AIDS-related illnesses worldwide (1). This is significantly less than the highest measured numbers in year 2005, when about 2.3 million people died (3). The reason for the falling numbers of deaths due to HIV/AIDS is explained by increased access to antiretroviral therapy and also that the numbers of persons newly infected by HIV are decreasing (3). However, the number of people living with HIV are rising due to growing populations, but also as a consequence of the antiretroviral medication that prolongs life for a lot of HIV positive people (4).

2.1.2 HIV in Tanzania

The Sub-Saharan Africa is the most HIV affected region in the world. Almost 70 % of the new HIV infections in the world, are found in this region (2). The decline of people dying from AIDS-related illnesses are however especially evident in this region due to the effects of antiretroviral treatment. In the African region, an estimated 1.1 million people died from HIV-related causes in 2013, 24% fewer than the 1.5 million in 2009. However, the African region was still home to about three in four people dying from HIV-related causes in 2013 (3).

The first cases of AIDS in Tanzania were discovered in 1983 and the disease has since then spread in all regions of the country (5). In 2013 there was an estimated 1.4 million people living with HIV in Tanzania and the prevalence of HIV was 5.0% in adults between 15-49 years. There was in this year 78,000 deaths due to AIDS in the country (6). The transmission of HIV in Tanzania is mainly caused by heterosexual intercourse and mother to child transmission (MTCT) (5). In November 2004 the Ministry of Health and Social Welfare initiated a nationwide program that focus on improving the access to care and treatment of HIV. The aim was to provide ARV for as many people as possible that are eligible for treatment, including home-based care for HIV patients (4).

2.1.3 Care and Treatment Clinics in Tanzania

The Care and Treatment Clinics (CTC) in Tanzania provides antiretroviral treatment, HIV prevention and support to HIV positive people. The clinics also have an important function in the education concerning the HIV infection, how it is transmitted, risk behavior and the treatment and progression of disease. The clinics provide regular counseling for patients who are on antiretroviral treatment (ART), in particular on treatment adherence. Regular monitoring of patients on ART, and the ART preparedness for patients who have not yet started ART are significant parts in the services of CTC (4).

This study was done at the Care and Treatment Clinic in the city of Dodoma, the official capital of Tanzania. About 2 million people are living in the region of Dodoma, about 300,000 in the urban areas (7). The prevalence of HIV in the region of Dodoma is 2.9 % (8). The CTC at Dodoma Regional Hospital provided in 2013 care for 8352 patients ≥ 15 years. The same year, 502 patients were newly initiated on ART at the CTC (9). The care and treatment services regarding HIV in Tanzania, including the cost of ARTs, are free of charge. The patients do not have to pay for the CTC visits or the medication, regardless of the level of

adherence to treatment. The HIV care and treatment is financed by The Global Fund (10) and the Ministry of Health and Social Welfare in Tanzania.

2.1.4 Antiretroviral treatment globally

ART consists in the standard treatment of at least three anti-HIV drugs suppressing the HIV replication. The therapy is important in order to control the virus, suppress the HIV infection and stop the progression of the disease. ART can reduce both mortality and morbidity and also improve the quality of life for HIV positive people (11). At the end of 2013, about 11.7 million people in low- and middle-income countries were receiving ART. This is an increase compared to a couple of years ago (2). However, the 11.7 million people receiving ART represent only 36% of the people living with HIV in low-and middle-income countries (12).

2.1.5 Antiretroviral treatment in Tanzania

According to the guidelines for treatment in Tanzania, the ART is initiated for patients with CD4 count < 350 cells/mm3 (regardless of clinical symptoms) and for patients in WHO stage 3 and 4 (regardless of CD4 count). The four groups of ARV used in Tanzania are NRTIs (nucleoside reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors), Nucleotide analogues (Nucelotide reverse transcriptase inhibitors), and Proteas inhibitors (PI). The recommendations consists of a combination of three drugs – 2 NRTI+1 NNRTI, 2 NRTI+1 PI or 3 NRTIs. Eight different triple combinations of drugs are recommended in the guidelines from the Ministry of Health and Social Welfare as the first line regimen, and the treatment is supposed to be considered to each individual with respect to side effects and interactions with other drugs.

The standard first line regimen in Tanzania is a combination of zidovudine (AZT), lamivudine (3TC) and efavirenz (EFV), and should be prescribed to all patients if there is no contraindication (4). A meta-analysis comparing the severity of adverse effects between

efavirenz (EFV) and nevirapine (NVP) concluded that EFV showed less severe adverse effects, with less frequency of drug discontinuation, than NVP. That supports efavirenz based combination treatment as the first line treatment regimens in the future (13).

2.1.6 Adherence

An essential component in the treatment of HIV is adherence to ART. In the National AIDS Control Program in Tanzania adherence is defined as follow: "Adherence to care is defined as a patient's ability to follow a care and treatment plan in the long term, attend follow up appointments as scheduled, take medications at prescribed times and frequencies, recognize side effects and seek treatment, and follow instructions regarding food and other medications, as well as avoid risk behaviors and practices such as drinking alcohol, having unprotected sex, etc."(4).

To reach satisfying results from the treatment the adherence to treatment needs to be > 95 %, which means high demands on the patients understanding and willingness to treatment (4). The adherence is the one most important factor to reach successful treatment. Just a few missed doses, leading to sub-optimal adherence, can be enough for the virus to replicate again and the virus in the blood increase. This can lead to development of resistance against the drug, and the regimen then has to be exchanged. Since cross-resistance between drugs is not uncommon, the drugs for treatment can be substantially limited as a consequence of poor adherence (14).

Different factors influencing adherence have been identified. Access to a clinic monitoring the treatment, daily routines concerning the medication and the patients´ understanding of the consequences of poor adherence are some important factors (4). An increase in social support for HIV positive patients has been seen to be positively associated with adherence in a study done in Indonesia. The family and friends are believed to play an important role in reminding

the patients to take their medication, help them to collect drugs and minimize the social isolation and stigma that can occur with a HIV diagnosis (15). Some studies have also shown that adherence is mainly affected through negative coping mechanisms such as use of alcohol, denial and self-stigma rather than positive coping mechanisms. One way to improve adherence could then be to reduce these negative coping mechanisms (16).

2.1.7 Adverse effects

Another challenge regarding the ART is the adverse effects that occur from the treatment. They can be divided into three categories. The first category consists of less severe and transient symptoms such as nausea, mild gastric symptoms, gentle headache and CNS disturbances. The treatment does not usually need to be stopped due to these symptoms. The second category contains more severe symptoms such as more severe nausea and vomiting, more severe gastric upset and headache and mild neuropathy. Symptomatic treatment is often enough, and the ART is seldom interrupted. In the third category even more severe symptoms can be found. More severe peripheral neuropathy, severe anemia and hypersensitive reactions to NVP (including liver effects and severe skin rashes) are some examples from this category. These adverse effects results in interruption of the ART and replacement by another regimen (4). It has also been noticed that some ARTs can cause metabolic complications such as dyslipidemia, insulin resistance and cardiovascular diseases. The effects on the kidney due to ART have been discussed, and particularly tenofovir (TDF) has been associated with kidney injury (17).

2.2 Aim

The aim of this study was to examine how the antiretroviral therapy (ART) among HIV positive patients is functioning, and to investigate potential differences between men and women, at a Care and Treatment Clinic (CTC) in Dodoma, Tanzania.

2.3 Specific Objectives

To analyze the following factors in patients on ART:

- The level of self-reported adherence among patients undergoing ART and factors associated with suboptimal adherence.
- The proportion of patients experiencing positive effects and adverse effects from ART, and if the adverse effects seem to influence the adherence.
- The accessibility and availability to the CTC as reported by patients.
- The effects on the patients' economy due to HIV.
- The level of knowledge of HIV transmission and the awareness among the patients of the importance of high adherence.

2.4 Medical relevance

HIV is one of the most severe diseases in the world. Many people globally and in Tanzania are affected by HIV. The treatment with antiretroviral medications has revolutionized the life for HIV positive people. The medication has led to reduced mortality and morbidity due to HIV and HIV positive people experience prolonged life compared to before the antiretrovirals (ARV) were introduced. However there are still some challenges concerning the antiretroviral treatment. To reach satisfying results from the treatment the adherence needs to be > 95 %. This is a very high level of adherence and requires a lot of understanding and commitment from the patients. There are also problems with toxicity and side effects of the antiretrovirals that affects many patients worldwide. Following this, it is of great importance to investigate how well the antiretroviral therapy is working in order to achieve adherence to treatment and to be able to reach successful results in the treatment of HIV patients.

It is also interesting to investigate potential differences between sexes regarding the treatment. The outcome of therapy and adverse effects can possibly differ between men and women and

it is important to not assume that the outcomes are exactly the same between sexes. Possible differences may for example exist since the women are screened for HIV during pregnancy, while the men do not have equivalent contact with the care and treatment services. Adverse effects may also differ since women tend to have a lower body weight compared to the men, but the doses of medication are the same regardless of weight. These are only a few examples of why it is interesting to compare men and women regarding the antiretroviral treatment.

This study was done to be able to identify parameters of importance for the outcome of therapy, and thereby be able to improve the treatment of HIV-positive people in Tanzania. It also involved investigation of the knowledge about the disease and how it is transmitted in order to be able to make prophylactic efforts to reduce the number of people infected by HIV. Hopefully, the results and conclusions from this study will make a small contribution to the future work with improvements in Dodoma.

3. Methodology

3.1 Study design

The study was done as a cross-sectional study on consecutive patients at a Care and Treatment Clinic of Dodoma Regional Referral Hospital in Dodoma, Tanzania. The patients answered a self-administered questionnaire and information was also collected from the medical records. The questionnaires contained 34 questions about patient characteristics and the antiretroviral treatment, regarding for example sociodemographic factors, adherence and accessibility to the clinic. From the medical records, which were completely written in English, information was collected such as date for initiation of ART, date for HIV diagnosis, CD4 levels and current ART regimen.

3.2 Study population

The participants of the study consisted of 200 HIV positive patients registered at the clinic, 79 men and 121 women. The patients were asked to participate in the study when they were at their regular visit at the CTC. Participants were selected with the help of the medical records based on the inclusion criteria, see below. The contact with the patients was taken with the help of a nurse working at the CTC who was speaking both Swahili and English, and the patients were randomly invited to participate and giving their informed verbal consent. Excluded were those that refused to participate in the study or did not fulfill the inclusion criteria. Data about the number of patients that did not want to participate in the study was not collected, but there were a few patients in total.

3.3 Inclusion criteria

HIV-diagnosed

≥ 18 years of age

≥ 1 year of treatment with ARV

3.4 Pre-testing

The questionnaires used in the study (Appendix 1) were compiled and changes were done after views and opinions from the supervisors in both Sweden and Tanzania. The last version was sent to the supervisor in Tanzania who arranged with translations of the questionnaires from English to Swahili. The translation was reviewed by two different doctors working at the CTC, independent of each other. The questionnaires were then printed in about 15 copies and a pilot study was done at the CTC to evaluate the comprehension of the questionnaires and to be able to do corrections in order to avoid potential misunderstandings and errors in the final study. The questionnaires were redesigned a bit, some new translations done, and 10

additional patients were pre-tested before continuing. After the final corrections, the last version could be printed and the data used in the study could be collected.

3.5 Data analysis/Statistics

The collected data from the questionnaires and the medical records were entered in to Microsoft Excel 2010 and SPSS version 22. The data was then analyzed using SPSS. The limit of statistically significant result was put at a p-value less than 0.05 (Fisher´s Exact Test). Excluded from the analysis were patients that had not answered that specific question in the questionnaire, or where information from the medical records was missing. The adherence was estimated using the questions on 14 day recall. The number of times that a patient took the medication in the last 14 days was divided by the number of times the patient was prescribed to take the medication in the same period. If the patient took less than 95% of the medication as prescribed it was classified as non-adherent, and $\geq$ 95% was classified as adherent.

3.6 Ethical considerations

The participation in the study was voluntary and the patients could at any moment choose to leave the study without specific reason, and the patients could also choose not to answer a specific question. Information, written in Swahili, about the study and the conditions was given to the patients. There was no difference in the care and treatment offered to the patients based on if they took part in the study or chose not to participate. To guarantee confidentiality of the patients the questionnaires were marked with a figure that in a separate document was related to information found in the medical records concerning the patient. After completing the data collection these documents were destroyed.

4. Results

4.1 Sociodemographics

Table 1. Sociodemographic caracteristics of the 200 participants in the study.

		Men	%	Women	%	Total	%
Sex		79	40%	121	60%	200	**100%**
Education	Never been to school	2	3%	16	13%	18	**9%**
p=0.003	Primary school	50	63%	84	70%	134	**67%**
	Secondary school	19	24%	16	13%	35	**18%**
	High school	3	4%	3	3%	6	**3%**
	University/college	5	6%	1	1%	6	**3%**
Occupation	Unemployed	2	3%	11	9%	13	**7%**
p=0.070	Employed	16	21%	19	16%	35	**18%**
	Self-employed	22	28%	38	31%	60	**30%**
	Student	3	4%	2	2%	5	**3%**
	Peasant/farmer	26	33%	47	39%	73	**37%**
	Retired	9	12%	4	3%	13	**7%**
Marital status	Married	45	58%	19	16%	64	**32%**
p<0.001	Single	5	6%	26	22%	31	**16%**
	Divorced/separated	11	14%	17	14%	28	**14%**
	Widowed	5	6%	40	33%	45	**23%**
	Cohabiting	10	13%	7	6%	17	**9%**
	Boyfriend/girlfriend	2	3%	11	9%	13	**7%**
Living conditions	Own house	54	70%	71	60%	125	**64%**
p=0.227	Rented house/apartment	21	27%	40	34%	61	**31%**
	No stable place to live	2	3%	8	7%	10	**5%**

Table 1 describes the sociodemographic characteristics. In total 200 patients were included in the study, and the study population consisted of 60% women and 40% men. The age of the participants ranged between 18 to 78 years. The mean and median age was 48 and 49 years for the men respectively 42 and 40 years for the women. A majority of the participants had gone to primary school. There was a significant lower level of education among the women

(p=0.003), 13% of the women had never been to school compared to only 3 % of the men. A larger proportion of the men had a higher education level compared to the women, with 24% in secondary school and 6 % in university/college. There was also a significant difference in marital status between men and women (p < 0.001), 58% of the men were married compared to only 16% of the women.

4.2 Adherence

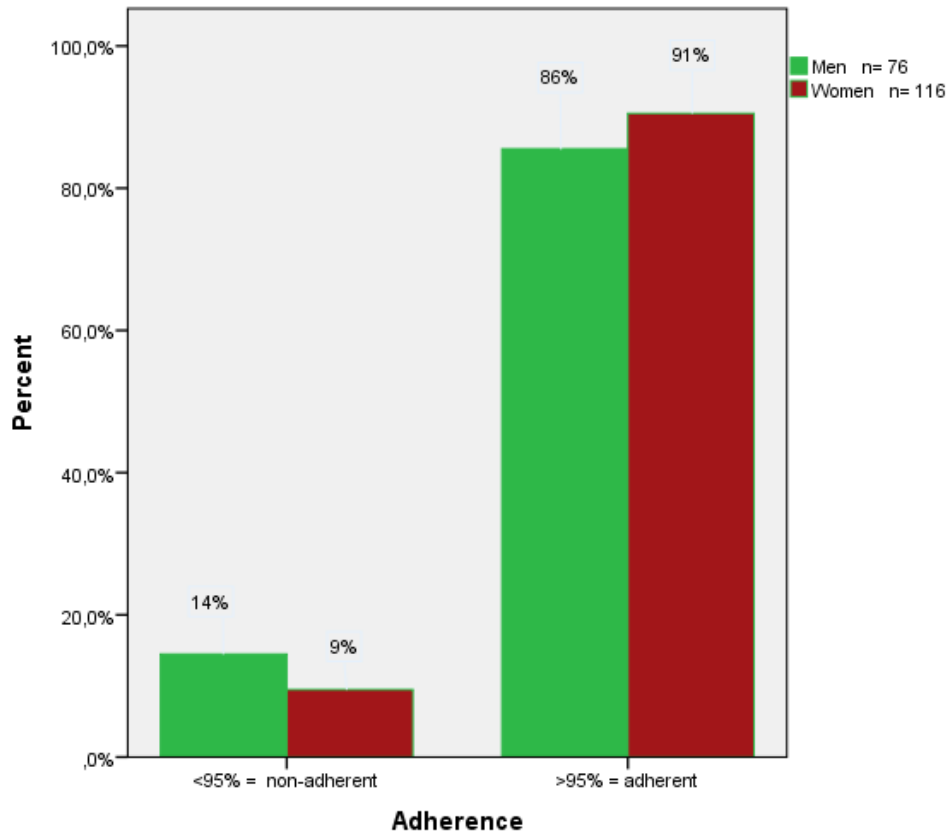

Figure 1. Adherence based on questions regarding 14 days recall. Patients with <95% adherence are classified as "non-adherent" and patients with > 95% adherence are classified as "adherent".

As seen in figure 1 the majority of the patients were classified as adherent to treatment using the 14 day recall method of self-reported adherence, 12 % of the patients were not adherent to treatment since they took less than 95% of the prescribed medication. The proportion of men

that was non-adherent to treatment was a bit higher than the proportion of women, but the difference was not significant.

The patients were also asked how many times in the last two weeks they had not taken the medicine, see figure 2. Most of the patients, 78 %, answered zero times which means that they had taken their medication as prescribed every day, 12 % reported that they had missed one time and 6 % had missed two times in the last two weeks. No significant difference was seen between men and women.

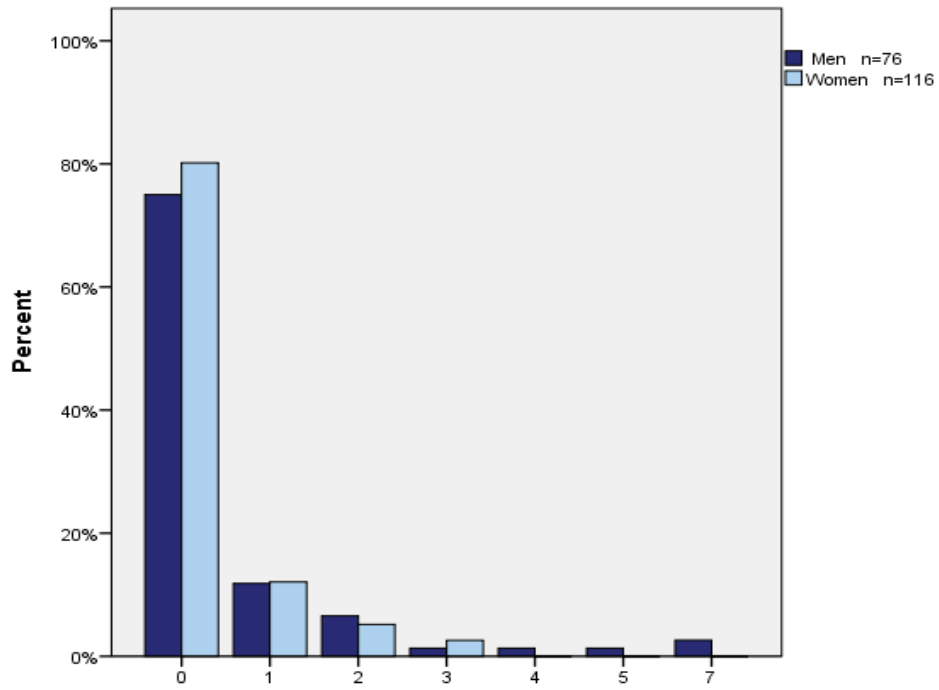

Figure 2. Number of times not taking the HIV drugs the last 14 days.

Questions about the reasons for taking the HIV drugs (reasons for adherence) respectively not taking the drugs (reasons for not adherent) were also analyzed. Table 2 shows the reason for adherence to treatment. As seen in the figure a great majority of the patients said that the main reason was to live longer. No significant difference was found between men and women ($p = 0.08$).

Table 2. The reason for taking the HIV drugs (reason for adherence)

		Men	Women	Total
What is the main reason for taking your HIV drugs?	To get cured from HIV	8	3	11
		10%	3%	6%
	To avoid getting symptoms of HIV	6	7	13
		8%	6%	7%
	The doctor tells me to take the medicine	1	1	2
		1%	1%	1%
	To live longer	63	109	172
		81%	91%	87%
Total		78	120	198
		100%	100%	100%

Table 3. The reason for not taking the HIV drugs (reason for not adherent)

	Men n=43	**Women n=46**	**Total n=89**	**P-value**
Simply forgot	56%	74%	**65%**	0.08
Not enough pills at home	16%	4%	**10%**	0.08
No time to get new pills	9%	2%	**6%**	0.19
Not enough money to get new pills	2%	4%	**3%**	1.00
No access to a clinic to get new pills	5%	0%	**2%**	0.23
Because of the side effects	7%	12%	**10%**	0.25
Other reason	21%	31%	**26%**	0.34

Table 3 shows the answer on the question "If you didn't take your medication at any point, what was the reason?". Most of the patients, 65%, said that the reason was that they simply forgot to take the pills. "Travelling" and "went to funeral" were the most common answers in the category "others". Men tended to report more often that they did not have enough pills at home, and more women answering that they simply forgot.

4.3 ART and adverse effects

Table 4. The current treatment with ART among the patients at the CTC.

		Sex		
		Men	Women	Total
Current treatment with ART	AZT+3TC+NVP	12	30	42
		15%	25%	21%
	AZT+3TC+EFV	27	34	61
		34%	28%	31%
	TDF+FTC+EFV	26	37	63
		33%	31%	32%
	TDF+FTC+NVP	0	1	1
		0%	1%	1%
	TDF+FTC+LPV/r	6	10	16
		8%	8%	8%
	TDF+FTC+ATV/r	4	4	8
		5%	3%	4%
	TDF+3TC+EFV	1	3	4
		1%	3%	2%
	AZT+3TC+LPV/r	1	1	2
		1%	1%	1%
	AZT+3TC+ATV/r	1	0	1
		1%	0%	1%
	ABC+3TC+ATV/r	1	0	1
		1%	0%	1%
	ABC+3TC+LPV/r	0	1	1
		0%	1%	1%
Total		79	121	200
		100%	100%	100%

The current antiretroviral combination regimens used among the participants in the study could be seen in table 4. Regarding the type of ARV used, there was no significant difference between men and women ($p = 0.66$). Nor was there any significant connection between type of ART and adherence ($p = 0.21$).

Regarding the number of times per day taking the ARTs, 38% of the patients were taking the medication 1 times a day, 60% two times a day, and 2% of the patients 3 times a day. There was no significant association between times per day taking the ART and adherence (p=0.43).

The proportions of patients with positive effects could be seen in table 5. A majority of the patients reported that their health status after started with ART was "much better" or "better". A very small portion of patients felt "the same" or "worse". More women said that their health is "much better", and a larger proportion of the men answered "better" compared to the women (p=0.03).

Table 5. The proportion of patients with positive effects of ART.

		Men	Women	Total
Compared to before you started treatment, how would you describe your health status now?	Much worse	1	0	1
		1%	0%	1%
	The same	0	1	1
		0%	1%	1%
	Better	33	32	65
		42%	26%	33%
	Much better	45	88	133
		57%	73%	67%
Total		79	121	200
		100%	100%	100%

The adverse effects of the treatment could be seen in table 6. Only 25% of the patients did not experience any adverse effect. About one fifth of the patients experienced nausea, rashes/skin lesions, reduced sensibility/numbness and muscle pain/joint pain. More men were suffering from diarrhea (p = 0.01). Otherwise, no significant difference between sexes could be seen. There were a lot of different answers in the alternative "others", e.g. loss of appetite, anxiety, back pain and fatigue.

Table 6. Adverse effects experienced by the patients in the last 6 months of treatment.

Adverse effects	Men n=78	Women n=121	Total n= 199	P-value
Nausea	22%	18%	**20%**	0.59
Vomiting	5%	2%	**3%**	0.21
Diarrhea	15%	3%	**8%**	0.01
Abdominal pain	17%	12%	**14%**	0.40
Rashes/Skin lesions	18%	20%	**19%**	0.85
Nightmares	17%	13%	**15%**	0.54
Problems to sleep	6%	10%	**9%**	0.45
Dizziness	15%	15%	**15%**	1.00
Reduced sensibility/numbness	22%	21%	**21%**	0.86
Fat loss in arms, legs or face	3%	6%	**5%**	0.49
Severe weight loss	9%	12%	**11%**	0.50
Muscle pain/joint pain	19%	17%	**18%**	0.70
Other	5%	9%	**8%**	0.41
No adverse effects	23%	26%	**25%**	0.62

Table 7. Adverse effects in relation to adherence.

		Adherence		
		<95% = non-adherent	>95% = adherent	Total
	Any adverse effect	20	121	141
		91%	72%	74%
	No adverse effect	2	48	50
		9%	28%	26%
Total		22	169	191
		100%	100%	100%

The connection between type of ART and the incidence of any side effect was investigated, but no significant correlation could be seen ($p = 0.93$). When comparing EFV-based regimens with NVP-based regimens, more of the patients with EFV-based regimens were suffering from nightmares, 17 % compared to 5 % of the patients on NVP-based treatment ($p=0.04$). There were no significant differences found regarding the incidence of dizziness, problems to sleep or rashes/skin lesions.

As seen in table 7, the non-adherent patients had a tendency towards more adverse effects, 91% compared to 72 % among the adherent patients (p = 0.07).

4.4 ART and CD4 level

Table 8 shows the latest measured CD4 levels, 15 % of the patients had current CD4 levels below 200 cells/mm3. More men had lower CD4 levels (p=0.005).

Table 8. Latest CD4 levels.

		Men	Women	Total
Latest CD4 level	0-199	14	15	29
		18%	12%	15%
	200-399	37	37	74
		47%	31%	37%
	400-599	21	37	58
		27%	31%	29%
	≥ 600	7	32	39
		9%	26%	20%
Total		79	121	200
		100%	100%	100%

The difference in CD4 cell counts between the latest value and the level when started ART can be seen in figure 3. All but eight of the men and eight of the women have risen in CD4 since started treatment. Most of the patients have risen with about 200-250 cells/mm3. Mean = 264, median = 209, range -239 to 1027.

The mean time of duration of ART was in this study 58 months.

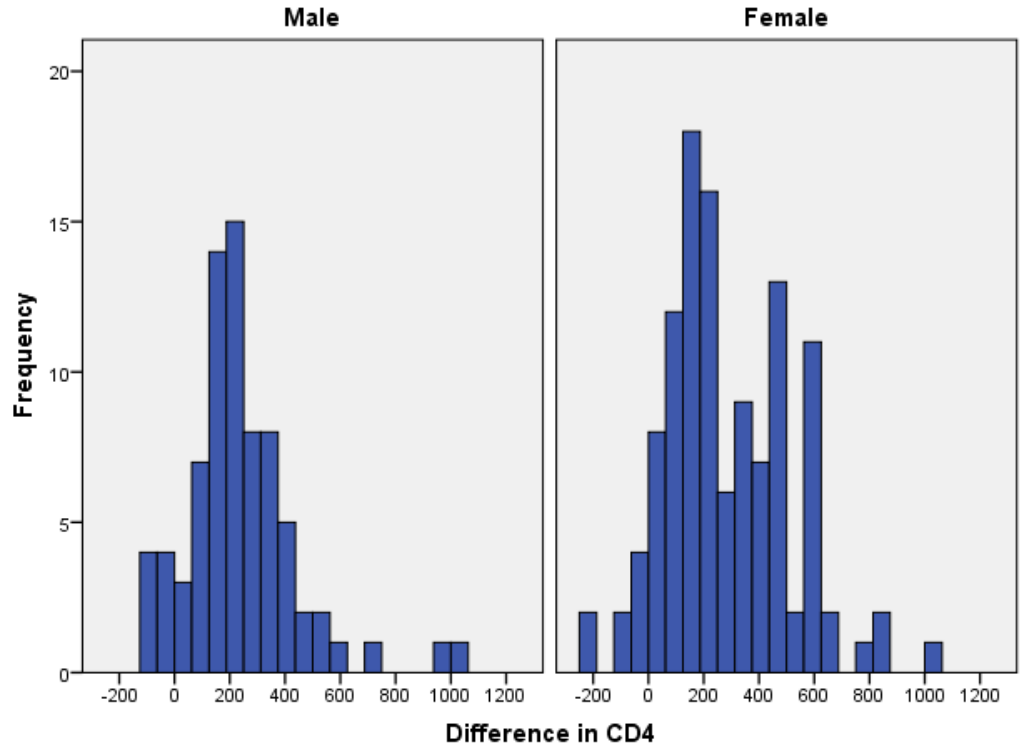

Figure 3. The difference in CD4 since the start of ART.

The difference in CD4 between the latest and the highest measured value could be seen in table 9. Among 40% of the patients the latest CD4 value was also the highest (the difference = 0). The other 60% of the patients had decreased in CD4 since the highest measured. Only the ones who had decreased in CD4 more than 200 cells/mm3 have been analyzed here. In total, 21 % of the patients had decreased in CD4 more than 200 cell/mm3. There was no significant difference between men and women (p = 0.48).

Table 9. Difference in CD4 since the highest measured value.

CD4 difference	Frequency	Percent %
<-200	41	21
>-200	159	80
Total	200	100

4.5 Knowledge about HIV

Table 10. Believed routes of HIV transmission. The percentage shows the proportion of correct answers,

Correct answers	Men n= 78	Women n = 121	p-value	Total n= 199
Shaking hands (no)	100%	100%	-	**100%**
Kissing (no)	91%	98%	0.05	**95%**
Sharing the same food/drink (no)	100%	100%	-	**100%**
From mother to child during pregnancy/breastfeeding (yes)	51%	66%	0.04	**60%**
Having sex with condom (no)	97%	98%	0.65	**98%**
Having sex without condom (yes)	95%	93%	0.57	**94%**
Through blood, e.g. needles, transfusion of blood (yes)	76%	73%	0.74	**74%**
Insects/mosquito bites (no)	99%	98%	1.00	**99%**

The knowledge about the routes for transmission could be seen in table 10. The knowledge was not good regarding "mother to child-transmission" and "through blood". Fewer of the men new about mother to child transmission, and more of the men thought that kissing was a route of transmission.

On the question "Are there any ways to cure HIV/AIDS?" 58 % of the patients chose the correct answer ("no"), 34 % did not know and 9 % thought that HIV was curable. There was no significant difference between men and women.

The information to the patients about the importance of adherence was good, 85% had got the information multiple times with detailed information. No significant difference between sexes. The awareness of high adherence among the patients showed that men had a lower knowledge than women about the fact that the ART could stop working if the adherence was poor (59% out of 78 men compared to 74% out of 121 women, $p = 0.03$). However, about 80% of both the men and the women knew that the symptoms of HIV could come back or increase due to poor adherence.

4.6 Economy, availability and accessibility

Regarding the availability and access to the clinic, 94 % of the patients answered that the availability/access was good. Only 6 % thought that it was difficult to contact the clinic and get a visit to the CTC. No significant difference was found between men and women.

Table 11. Ways of travelling to the CTC and economic costs for travelling.

		Men	%	Women	%	Total	%
How do you travel to get to the clinic? (p=0.001)	Walking	16	20%	28	23%	44	**22%**
	By car	21	27%	36	30%	57	**29%**
	By bus	27	34%	54	45%	81	**41%**
	By bicycle	9	11%	0	0%	9	**5%**
	By motorcycle	6	8%	3	3%	9	**5%**
How long time do you travel to the clinic? (p=0.136)	<30 min	25	32%	21	17%	46	**23%**
	30 min - 1 hour	29	37%	45	37%	74	**37%**
	1 hour - 2 hours	15	19%	36	30%	51	**26%**
	3 hours - 4 hours	7	9%	11	9%	18	**9%**
	>4 hours	3	4%	8	7%	11	**6%**
How big are the economic costs of travel to the clinic for you? (p=0.128)	Not mentionable	5	6%	6	5%	11	**6%**
	Low	20	26%	27	22%	47	**24%**
	Moderate	41	53%	59	49%	100	**50%**
	High	12	15%	20	17%	32	**16%**
	Not bearable	0	0%	9	7%	9	**5%**

Table 11 shows that most of the patients, 41% came to the CTC by bus. More men were travelling by bicycle and motorcycle and a greater proportion of women came by bus. In total, 15% of the patients had travelled more than three hours to get to the clinic. As much as 80 % of the patients experienced the costs of travelling as moderate, low or not mentionable. However, about 20% answered that the costs were high or not even bearable. A majority of the patients, 94%, had never let down their medication due to economic consequences. No significant difference was seen between sexes.

As seen in table 12, a tendency could be seen towards more men with negative impact on their economy compared to the women (p = 0.073), 46% of the men said that living with HIV had made their economy worse.

Table 12. Economic impact due to HIV.

		Men	Women	Total
Do you think that living with HIV has made your economy worse than if you were all healthy?	Yes	36	39	75
		46%	32 %	38%
	No	43	82	125
		54%	68%	63%
Total		79	121	200
		100%	100%	100%

Among the patients that answered that HIV had made their economy worse, the reason for this was reported by the patients, see figure 4. No significant difference was found between men and women.

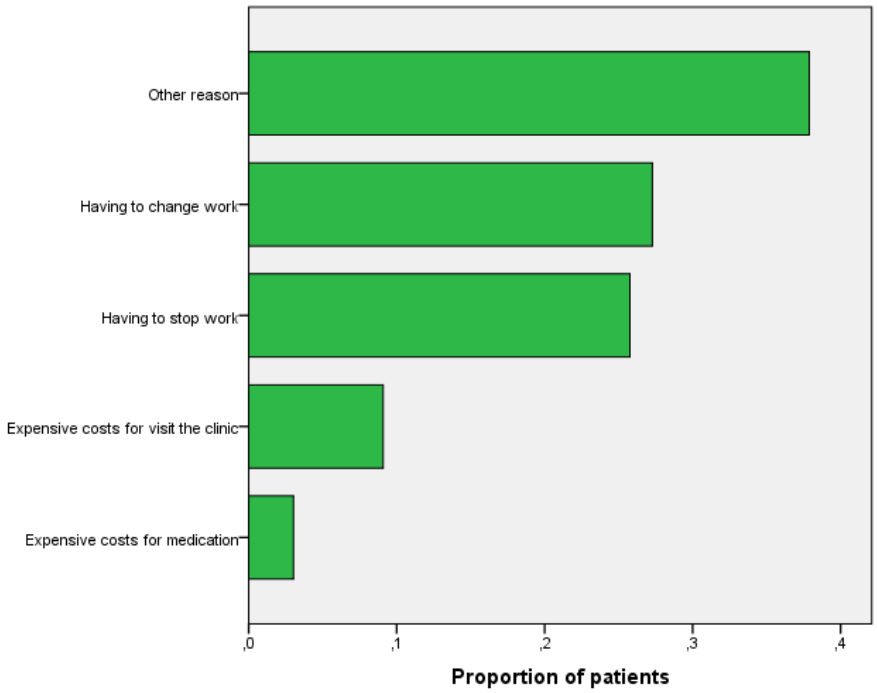

Figure 4. The reason for worsening of the economy due to HIV (n=66). The most common answer in "other reason" was that HIV had made the health worse, which negatively affected the ability to work.

5. Discussion

5.1 Sociodemographic factors

The participants in this study had mainly gone to primary school (67%). However 9 % of the patients had never been to school. Regarding to statistics from Unicef, the enrolment ratio in primary school is 98.2% in Tanzania (18). Since the mean age in this study was 48 (men) and 42 (women) years, it is possible that the enrolment ration in primary school was lower a couple of decades ago. The attendance ratio in secondary school is now between 24-26 % (18). In this study only 18% had gone to secondary school. The education level was in general higher for the men compared to the women.

Regarding the marital status, more of the women were single or widowed compared to the men. It could be speculated that this is because their former partners have already passed away in HIV/AIDS. Since women tend to be married to slightly older men, and the most common route of transmission for adults in Tanzania is through heterosexual intercourse, this could be an explanation. The larger proportion of women being single compared to the men can be speculated about as well. Possibly, it is more difficult for HIV positive women to find a new partner when living with HIV. A recent study about the association between HIV status and marriage dissolution suggested that there were difference between sexes. Higher HIV prevalence was more common among formerly married women compared to formerly married men (19).

5.2 Adherence

The level of self-reported adherence in this study was 88 %. Adherence was in this case defined as patients taking more than 95 % of the medication, and these patients were classified as adherent to treatment. A meta-analysis regarding the adherence levels in Sub-

Saharan Africa (SSA) compared to North America showed 77 % adherence levels in SSA (20), which indicates lower levels of adherence compared to this study. However, there is a broad variation of adherence level between different studies, and the adherence in this study is consistent with other studies done in Tanzania (21-23) with similar levels. It is important to consider the possibility that many of the patients with high adherence are the ones that are still attending the CTC, while the ones with low levels of adherence might have a lower attendance to the clinic. Patients with very low adherence to treatment are more likely to drop out from the care and treatments offered by the CTC, and also have a higher risk of mortality in the long term. Since these patients are not included in the study there is some risk that the level of adherence is overestimated.

The results also showed that 78% of the patients had taken their medication every day, and a falling percentage scale had missed 1, 2, 3 times and so on in the last 14 days. The relatively high levels of adherence and low levels of missed doses found in this study are of course beneficial for the outcome of therapy. The adherence is crucial for the success of ART and suboptimal adherence leads to resistance to ARV, immunological decline and quicker progression of the disease (21). The most frequent reason for being adherent was to live longer, 6 % answered to get cured from HIV. Since HIV is not curable, this could indicate a poor knowledge among the patients considering this. The reason for not taking the HIV drugs (not being adherent to treatment) was mainly forgetfulness. The second most common answer was “other reason”, for instance travelling and going to funeral. Travelling, transport costs and forgetfulness have also been mentioned as common reasons for not taking the medication in other studies (24). Regarding the factors for suboptimal adherence that were investigated, no statistical association was found with sex, type of ART combination regimen, number of times per day taking the ART or the presence of adverse effects from the treatment. There was

however a tendency towards association between the presence of adverse effects and low adherence. This connection has been found in several previous studies as well (24, 25).

5.3 Positive effects and adverse effects

The positive effects on health since starting the antiretroviral treatment were in a great majority of the patients prominent. All but two of the patients answered that their health status had become better or much better. This means that the ART can be considered as successful for most of the patients with good treatment outcome. Women tended to choose "much better" more often than men, but the underlying reason for this is hard to know. Despite improvement of health status when being on ART, a great proportion of the patients were also suffering from adverse effects, 75% of the patients experienced any adverse effect. The most frequent symptoms were nausea, rashes/skin lesions, sensibility disturbances and muscle/joint pains. When putting together "nightmares" and "problems to sleep" the total proportion of patients becomes 24% experiencing effects on the sleep. Men experienced diarrhea for a greater extent than the women. The reason for this is not known, and there was no significant difference between sex and current ART that could explain the difference. More of the patients on EFV-based regimens had nightmares compared to the ones on NVP-based regimens. This could probably be explained by the CNS adverse effects caused by efavirenz (EFV) (4, 13). The known adverse effect of rashes/skin symptoms caused by nevirapine (NVP) (4, 13) did however not show any significant association in this study.

5.4 CD4 levels and antiretroviral treatment

Most of the patients in this study had a current CD4 value above 200 cells/mm3 and can be considered to have an effective treatment. However, 15% had a CD4 below 200 cells/mm3, which indicates that the treatment is not very successful. This can have several different reasons such as poor adherence to treatment resulting in decreased immunological response or

the development of drug resistance to the current treatment. Another possible reason is that the ART was initiated at a very late stage of HIV infection, with limited possibility to increase the CD4 levels. The baseline immunologic and clinical status has been found to be a significant predictor of HIV-related morbidity and mortality (26, 27).

The men tended to have lower CD4 levels in general, 18% had less than 200 cells/mm3 and a smaller proportion of the men had really high levels above 600 cells/mm3. The reason to this cannot be explained by lower adherence, difference in current ART or higher amount of adverse effects, since none of this had shown any significant differences compared to women in this study. A previous study from Tanzania has also shown that men were more immunosuppressed with CD4 levels lower than the women. Suboptimal adherence and advanced immunodeficiency at enrollment were some findings associated with this, but could not explain the whole difference (28). Since the women regarding to the guidelines in Tanzania is offered an HIV test when pregnant, the HIV infection can often be detected in an earlier stage (4). The men tend to have more advanced stage of HIV at disease presentation, which makes them less likely to respond well to ART, according to previous studies (29).

Besides the latest CD4 levels, the difference in CD4 was measured since started ART. This shows that a great majority of the patients had increased in CD4 since started ART, which can be considered as successful antiretroviral treatment (4). The results also showed that about 20 % of the patients had decreased in CD4 more than 200 cells/mm3 since the highest measured CD4 level. This could possibly show an ongoing treatment failure, indicating suboptimal adherence to treatment. However, the decrease in CD4 might also be a consequence of opportunistic infections or concomitant diseases resulting in low CD4 levels.

5.5 Knowledge

The knowledge about transmission routes for HIV through blood transfusion/needles was only 74%. Mother to child transmission (MTCT) was also less known, particular among the men. Only about half of the men knew about MTCT as a possible transmission route of HIV. Furthermore, 9% of the men thought that kissing transmitted HIV. These results cannot be completely satisfying, since most of the patients have been in the care and treatment services for a long period of time and should have got information about routes of transmission. Comprehensive knowledge of HIV in Tanzania is known to be somewhat lower for the men compared to women in statistics from Unicef (18). It can be speculated that the knowledge about MTCT is lower for the men since they are not that much involved in the care and treatment during pregnancy and breast feeding.

The men also had lower level of knowledge about the importance of high adherence, specifically that the ART could stop working due to suboptimal adherence. Since there was no significant difference between sexes regarding the information given about importance of adherence, this could not be a reason for differences between sexes. Difference in adherence could neither explain the differences of knowledge.

5.6 Economy, availability and accessibility

The accessibility and availability to the CTC experienced by the patients were good, even though 15% had travelled more than 3 hours. The costs of travelling were mainly considered as moderate-low, and could not be considered as a major obstacle for adherence or limited visits to the CTC. Possible economic consequences such as travel costs to get to the CTC and not be able to go to work did not affect the ability to take the medication, and economic limitations does not tend to result in suboptimal adherence. However, 38% of the patients said their economy were worse due to HIV. There was a tendency towards more men experiencing

negative effects on their economy. The main reason for this was being sick/weak which negatively affected the ability to work. One can assume that most of the men have the role as the major economic family supporter, and by this for a greater extent experienced the economic effects as a severe problem.

5.7 Strength and limitations

The strengths with this study could be described as follow. The use of questionnaires for answering the questions is a good way to be able to get as much confidentiality as possible. It is reasonable to believe that the patients answer more honestly when writing by themselves, instead of for example oral interview technique, especially when the questions were about HIV which is known to be associated with a lot of stigma. There was also a careful process when selecting the questions in the questionnaires. The translation was done by an English speaking doctor in Tanzania, and was re-checked by another Tanzanian doctor after the first translation, with some small corrections. Also the pre-testing phase was an important part in the methodology, which led to some small corrections, to make the questionnaires and the data collection as understandable and reliable as possible. The nurse that was involved in the distribution of questionnaires and oral instructions to the patients in Swahili, also contributed a lot to the feasibility of the study. Since the communication with the staff in English was easy no larger language barriers existed. Having the same person introducing the questionnaires and answering questions in Swahili could also be considered as a good way of avoid differences in the practical implementation of the study.

However, there are also multiple limitations regarding this study. First of all, the patient material is quite small and the study was only done at one clinic at one of the hospitals in Tanzania. This means that the generalizability of the results and conclusions are limited, and very likely the possibility to get significant results when analyzing the data could increase with a larger patient material. This was unfortunately not feasible in this study, since the time

for data collection was quite limited. Another limitation is that for practical reasons the study was done as an on-treatment analysis that only included patients still visiting the CTC. Following this, the adherence could not be estimated on all patients who were initiated on ART from the beginning. Some of the patients have probably dropped out from the care and treatment, moved to another city or even passed away. It is also possible that the patients with very low adherence are not coming to the CTC, and these patients are by this not included in the study. The use of 14 day recall as a way of estimating the self-reported adherence can also be discussed. There is of course a possible risk that the patients have been more aware of taking the medication when the visit at the hospital is close in time. However, 14 days recall concerning the adherence is a reasonable period of time measuring the self-reported adherence, since the risk of recall bias increases when using a period further back in time.

The use of methodology with distribution of printed questionnaires could also be discussed. While the possibility for confidentiality increases with patients filling out the questionnaires by themselves, it leads however to a selection of patients that knew how to read. Since the adult literacy rate in Tanzania is only 67.8 % (18), some patients are through this lost in the selection process. Sometimes when the participants could not read, a nurse helped them by reading the questions. Still, this was a limited amount of patients since the facilities and time was not enough to do this for a large amount of patients. Even the patients that knew how to read had sometimes still difficulties filling out the questionnaires, since they were not used to this kind of questions and ways of answering. This problem was limited by most of the time having a Swahili-speaking person available to assist the patients.

Even if the confidentiality rate increased by using questionnaires instead of interviews, the way of being anonymous was not really possible. The patients were sitting in the same room close to each other when answering the questions and the other participants could hear if one had any questions regarding the content. Unfortunately, this could not be avoided since the

small amount of space at the clinic and a large flow of patients visiting the CTC. The collection of data from the medical records also had some difficulties. Sometimes the patients were transferred from another CTC, which meant that information from earlier visits could not be found. The information from the medical records was not always complete with for example date for initiation of ART and initial CD4 value missing.

6. Conclusions

- The level of self-reported adherence was high among the participants in this study. No statistical association was found between suboptimal adherence and sex, type of ART or presence of adverse events.
- The majority of the patients experienced increased health status. However, 15 % had a CD4 level that was below 200 cells/mm3 and one fifth of the patients had decreased with more than 200 cells/mm3 compared to the highest measured level.
- Three out of four patients reported adverse events from ART. There was a tendency towards more adverse effects among the non-adherent patients.
- The patients reported good availability and accessibility to the CTC. Economic consequences were not a reason for suboptimal adherence. About 40% of the patients reported that HIV had a negative impact on their economy. The tendency was that more men than women experienced this negative effect.
- Men had a lower level of knowledge about HIV compared to the women.

7. Acknowledgements

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Last I would like to thank SIDA for making this project feasible by economic support through the scholarship.

8. Populärvetenskaplig sammanfattning

Hög följsamhet till antiretroviral behandling, trots många oönskade effekter bland människor som lever med HIV i Dodoma, Tanzania.

HIV är en virusinfektion som orsakar nedsättning av immunförsvaret hos den som smittats. Utan en fungerande behandling leder sjukdomen så småningom till allvarlig immunbrist och utveckling till sjukdomen AIDS. HIV orsakar stort lidande över hela världen. Ett av de värst drabbade områdena är länderna söder om Sahara, där förekomsten av och dödligheten i HIV är hög. I Tanzania lever 1,4 miljoner människor med HIV, och år 2013 var det totalt 78 000 dödsfall i sjukdomen till följd av AIDS.

Det finns så kallad ”antiretroviral” behandling som sänker virusnivåerna i kroppen, minskar risken att utveckla allvarliga symptom av sjukdomen och förlänger livet för många HIV positiva patienter. Följsamheten till behandling är emellertid av största vikt för att läkemedlen ska ha bra effekt. Det kräver att patienterna tar minst 95 % av medicinerna, d.v.s. inte missar mer än 5% av de ordinerade doserna.

Denna studie syftade till att undersöka hur behandlingen med antiretrovirala läkemedel fungerar på en HIV-klinik i Tanzania, med extra fokus på följsamheten till behandling.

Studiens metod innebar att patienterna på kliniken fick besvara en enkät med frågor som berörde olika aspekter av den antiretrovirala behandlingen, däribland följsamhet till behandling. Totalt ingick 200 patienter i studien. Uppgifter om olika lab-värden, behandlingstid med mera inhämtades också från journaler.

Resultaten visade att den antiretrovirala behandlingen som helhet fungerade väl utifrån de förutsättningar som gavs. Hela 88 % av patienterna var följsamma till behandlingen, vilket är

en relativt hög andel. Detta trots att så många som 75 % av patienterna upplevde oönskade symptom som sannolikt kan kopplas till behandlingen. Att ta reda på orsakerna till varför vissa patienter inte är följsamma till behandling är viktigt för att på sikt kunna förbättra effekterna av behandlingen. Ett resultat av denna studie visade att den vanligaste orsaken till att man inte tog läkemedlen helt enkelt var glömska. Det fanns även en viss tendens till att de patienter som inte var följsamma till behandlingen upplevde negativa symptom i större utsträckning. Studien kunde även påvisa en del skillnader mellan män och kvinnor, där männen generellt hade sämre kunskap om HIV och hade lägre nivåer av immunceller kallade CD4-celler. Det fanns även en tendens till att männen i större utsträckning upplevde en negativ påverkan på sin ekonomi som en följd av HIV-diagnosen.

Framöver kan det vara intressant att ytterligare undersöka eventuella skillnader mellan män och kvinnor i en studie med större patientmaterial och en längre observationstid. Detta för att i framtiden kunna göra ännu fler förbättringar avseende den antiretrovirala behandlingen och riktade åtgärder för enskilda individer som står på behandling mot HIV.

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Appendix 1 - Questionnaire

Antiretroviral treatment of HIV in Dodoma, Tanzania

This is a questionnaire concerning the HIV treatment that you undergo. This is a part of my master thesis as a medical student in Sweden, and will examine how the HIV treatment in Tanzania is functioning. The participation in the study is voluntary and confidential. You can choose to leave the study without specific reason. There will be no difference in the care and treatment offered to you based on if you take part in the study or not. I hope that you want to participate in the study!

Instructions: Please tick the boxes for the appropriate answer. For some questions, more than one alternative can be chosen. Where a longer answer is required, please fill in your answers in the space provided.

A. General questions

1. **Age:** _____ years
2. **Sex:**
   - Male
   - Female
3. **Level of education:**
   - Never been to school
   - Primary school
   - Secondary school
   - High school
   - University/College
4. **Occupation:**
   - Unemployed
   - Employed
   - Self-employed/business
   - Student
   - Peasant/ farmer
   - Retired
5. **Marital status:**
   - Married
   - Single
   - Divorced/Separated
   - Widowed
   - Cohabiting
   - Boyfriend/girlfriend
6. **Living conditions:**
   - Own house
   - Rented house/apartment
   - No stable place to live

B. Treatment

7. **What is the main reason for taking your HIV drugs?**
   - To get cured from HIV
   - To avoid getting symptoms of HIV
   - The doctor tells me to take the medicine
   - To live longer
8. **Compared to before you started the treatment, how would you describe your health status now?**
   - Much worse
   - Worse
   - The same
   - Better
   - Much better

9. **How many pills for HIV treatment are you prescribed per day?**
   _____pills
10. **How many of the prescribed pills for HIV treatment did you take yesterday?**
    _____pills

11. **Have you experienced any of the following symptoms the last 6 months? (you may choose several options)**
    - Nausea
    - Vomiting
    - Diarrhea
    - Abdominal pain
    - Rashes/skin lesions
    - Nightmares
    - Problems to sleep
    - Dizziness
    - Reduced sensibility/ numbness in arms or legs
    - Fat loss in arms, legs or face
    - Severe weight loss
    - Muscle pain/joint pain
    - Other_____
    - No bad symptoms
12. **If yes, do you believe that the symptoms are due to side effects of your medical treatment?**
    - Yes
    - No
    - I don't know
13. **Have you at any time not taken your medicine due to side effects from the medication?**
    - Yes, many times
    - Maybe some time
    - No, never
14. **How many times per day do you take your HIV drugs?**
    - 1 times a day
    - 2 times a day
    - 3 times a day
15. **In the past 14 days how many times did you not take your medication as prescribed?**
    _____times
16. **If you didn´t take your medication at any point, what was the reason? (You may choose several reasons)**
    - Simply forgot
    - Did not have enough pills at home
    - Did not have time to get new pills
    - Did not have enough money to get new pills
    - Did not have access to a clinic where I could get the pills
    - Because of the side effects (please specify)_____
    - Other reason_____

C. <u>Accessibility, availability, economy</u>

17. **How do you travel to get to the clinic?**
    - Walking
    - By car
    - By bus
    - By bicycle
    - By motorcycle

18. **How long time did you travel to get to the clinic?**
    - Less than 30 minutes
    - 30 minutes – 1 hour
    - 1 hour – 2 hours
    - 3 hours - 4 hours
    - More than 4 hours
19. **How big are the economic costs of travel to the clinic for you?**
    - Not mentionable
    - Low
    - Moderate
    - High
    - Not bearable
20. **How is the availability/access to the HIV-clinic?**
    - It is easy to contact the clinic and get a visit there when I need to
    - It is hard to get a visit and to contact the clinic
21. **Do you have to pay for your HIV medicine?**
    - Yes
    - No
22. **Have you ever let down your medicine due to economic consequences? (For example costs to get to the clinic, costs to get the pills, have to stay home from work etc.)**
    - Yes, often
    - A few times
    - No never
23. **A. Do you think that living with HIV has made your economy worse than if you were all healthy?**
    - Yes
    - No

23 **B. If yes, what do you think is the reason?**

- Expensive costs for medication
- Expensive costs for visit the clinic including doctor visits
- Having to stop working due to HIV
- Having to change work due to HIV
- Other_____

D. <u>Knowledge of HIV and HIV drugs</u>

24 **How do you think HIV is spread from one person to another? (you may choose several options)**
- Shaking hands
- Kissing
- Sharing the same food/drink
- From mother to child during pregnancy/breastfeeding
- Having sex with use of condom
- Having sex without condom
- Through blood, e.g. needles, transfusion of blood
- Insects/mosquito bites

25 **Are there any ways to reduce the risk to get infected by HIV?(you may choose several options)**
- Use condoms – safe sex
- Abstain from sex
- Medicine to mother during pregnancy and breastfeeding
- Male circumcision

26 **Are there any ways to cure HIV/AIDS?**
- Yes
- No
- I don´t know

27 **If you don´t take the HIV drugs continuously, may any of the following negative consequences occur from this?(you may choose several options)**
- The symptoms of HIV may return/increase
- The HIV drugs can stop working
- You can transmit HIV to others more easily

28 **Have you got information about the importance of taking the HIV drugs regularly and why it is important?**
- Yes, multiple times with detailed information
- Yes, a few times
- Yes, but only one time when I started treatment
- No, I never got the information
- I don´t know

E. <u>Contact with partners</u>

29 **Do you know your partners HIV status?**
- Yes, positive
- Yes, negative
- No, I don't know
- I have no current sexual partner. (only answer question 33)

30 **Do you have sexual relationships with more than one partner?**
- Yes
- No

31 **If yes, how many sexual partners do you have? (please specify with a number)**

_____

32 **Do you use condom during sex?**
- Yes, always
- Most of the times
- Not very often
- No, never

33 **The last time you had sex, did you use a condom?**
- Yes
- No
- I do not remember

34 **With which sexual partners have you been using condoms?**
- Regular partner
- Temporary partner
- All sexual partners
- I do not use condoms

Thank you very much for your participation!

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