# *Caregiver trust: a positive influencer for medical appointment attendance?*

The association of caregiver trust, distance to clinic, and health literacy on medical appointment attendance rates of people living with HIV in rural South Africa


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**Abstract**

*Introduction*: Access to antiretroviral therapy (ART) has rapidly expanded globally. In South Africa 3,3 million people are currently receiving ART. Adherence is critical for successful ART; even minor non-adherence can have major consequences for treatment success. Medical appointment attendance (MAA) is an important predictor of ART adherence, but evidence regarding predictors of MAA is limited, particularly from rural areas. This study focuses on three hypotheses: (1) caregiver trust is positively associated with MAA, (2) distance to clinic strengthens this effect and (3) health literacy mediates this effect. *Methods*: Self-report data, including questions regarding illness, lifestyle, weight measurements, blood tests, alcohol use and current medicines were collected at entry into the ITREMA trial in the rural area of South Africa. The purpose of the ITREMA trial was to see the effects of intensified treatment monitoring. Data were analysed in SPSS, using logistic regression analyses and Hayes' PROCESS macro. *Results*: 501 patients filled in the ITREMA baseline questionnaire, of whom 422 remained in care and attended their medical appointments through their participation in the study, while 78 became lost to follow-up (LTFU). Men, younger people and people reporting lower caregiver trust were more likely to become LTFU. Health literacy was found to partially mediate the association between caregiver trust and MAA. *Conclusions*: This sample in rural South Africa indicated a positive association between caregiver trust and MAA, with health literacy as a partial mediator of this association. Distance does not strengthen the effect between caregiver trust and MAA. Men and younger patients may need additional support to reduce LTFU rates. More data in the same settings are required to enable the results of different studies to be able to generalize this results.

## Introduction

When it comes to public health, one concerning subject stands out clearly since the 1980s, and that is the epidemic of the worldwide human immunodeficiency virus (HIV) (Healthline, 2016). According to the World Health Organization (2017) HIV has claimed more than 35 million lives so far. In addition, one million people have died from HIV-related causes, and currently 36.7 million people are living with HIV. And this is not the end; there were 1.8 million people newly infected in 2016. Approximately 70% of HIV-infected people are living in Africa, which makes it the most affected continent. Among the African countries, South Africa remains the country with the largest number of HIV and acquired immunodeficiency syndrome (AIDS) (Shisana et al., 2005). Furthermore, South Africa also has the highest rate of new HIV infections (Maurice, 2014); in 2016, South Africa reported approximately

270,000 new HIV cases and around 110,000 AIDS-related deaths (UNAIDS, 2018). The estimate of HIV-infected people in South Africa is 7.1 million; therefore, about 12.8% of the 55.5 million people living in South Africa are infected (Statistics South Africa, 2018). Patients who are infected by HIV are treated with antiretroviral therapy (ART), this is a combination therapy which prevent the virus from reproducing (Hammer et al., 2006). Fifty-four percent of adults and 43% of children with HIV are currently receiving ART. Due to the ongoing rise in new HIV infections more people are faced with a complex ART regime (Worldwide AIDS & HIV statistics, 2010).

Nowadays, people with HIV and AIDS can possess the same life expectancy as non-infected people if the HIV-positive individuals strictly adhere to ART (Clayson, et al., 2006; Deeken, Pantanowitz & Dezube, 2009). South Africa has spent great effort in its response to HIV and AIDS; 3,3 million people are receiving ART. This is the largest HIV and AIDS treatment program in the world, which has resulted in a decline of AIDS-related deaths over 55% (UNAIDS, 2017). Since ART is widely available in South Africa, it becomes more important to strive for improved ART adherence. Non-adherence is a multidimensional health problem which is related to social and behavioural factors due the fact that the behaviour of patients is involved. Causes of non-adherence may be related to patient, treatment and/or healthcare provider (Hugtenburg, Timmers, Elders, Vervloet, 2013). This study concerns medical problems that require social science knowledge to get a better understanding of patient behaviour.

A very important influencer of ART adherence is medical appointment attendance (MAA) (Catz, McClure, Jones & Brandtley, 1999). Another influencer of ART adherence is the trust and relationship with the doctor (Cruz & Pincus, 2002; Lacro, Dunn, Dolder, Leckband & Jeste, 2002; Weiss, Smith, Hull, Piper & Huppert, 2002). This study intends to discover if there is a connection between caregiver trust and MAA. Studies regarding caregiver trust and MAA are scarce, especially in rural areas. In addition, earlier studies regarding the effect of caregiver trust on MAA has not been found. Thus, a question emerges on how MAA is influenced by caregiver trust, with the purpose of achieving better ART adherence and less HIV and AIDS related deaths.

## Theoretical exploration

### *Treatment of HIV and AIDS*

A few decades ago, the life expectancy of people infected with AIDS was three years (Healthline, 2016). At present, HIV patients can have the same life expectancy as healthy

individuals due to the introduction of ART (Clayson et al, 2006). ART does not cure the patient, but ART makes it a treatable chronic disease (Deeken et al., 2009). Crucial for this is therapy adherence, which ensures patients do not deviate from the treatment scheme (Crum et al., 2006; McDonald, Garg & Haynes, 2002). Even minor non-adherence in HIV treatment can have major consequences for treatment success (Montaner et al., 1998; Krummenacher, Cavassini, Bugnon & Schneider, 2011).

Despite the overwhelming health benefits of ART, many patients struggle with adherence (Hill & Kavookjian, 2012). Research estimates that 50% to 70% of ART users are not fully adherent in their first six months of treatment (Simoni, Pearson, Pantalone, Marks & Crepaz, 2006). To reach the desired health outcomes and restrict HIV-related deaths, research should focus on behavioural intentions to maintain motivation for optimal ART adherence. ART adherence is *the* key mediator between medical practise and patient outcomes (Kravitz & Melnikow, 2004).

*Medical appointment attendance (MAA)*

MAA refers to the degree of sticking to the medical appointments. Patients in rural South Africa get their treatment during their appointment, which makes MAA very important (Catz et al., 1999). Consistent attendance plays a central role in the health of people living with HIV. Patients who do not have a routine in their medical appointments cannot fully benefit from the available treatment (Catz et al., 1999). Patients are considered as 'lost to follow-up' (LTFU) if they have not come back to the clinic within 90 days of their last, missed clinical visit (Shepherd et al., 2013).

Different factors related to non-adherence to MAA have already been found. Non-adherence to MAA has been associated with a young age, less severe illness and lower perceived social support (Catz et al., 1999). It is not clear yet if caregiver trust, also a form of support (Ciechanowski, Katon, Russo & Walker, 2001), has a significant effect on MAA. Moreover, MAA is a less investigated issue. In this research, the focus is on the association between caregiver trust and MAA. Different forms of social support are also related to ART adherence; cross-sectional data and studies on HIV patients receiving ART have shown that greater social support leads to better ART adherence and MAA (Gonzalez et al., 2004, Catz, Kelly, Bogart, Benotch & McAuliffe, 2000; Catz et al., 1999), whereas less satisfactory social support leads to poorer ART adherence (Singh et al., 1999). This study intends to examine if caregiver trust is associated with MAA.

*Caregiver trust*

Caregiver trust is a subject of increasing focus, probably because of the constant finding between doctor-patient relationship and ART adherence (Cruz & Pincus, 2002; Lacro et al., 2002; Weiss et al., 2002). Caregiver trust implies that there is an effective relationship between the provider, for example the doctor, and the patient that is based on empathy, attentiveness, care, concern and support (Ciechanowski et al., 2001). The doctor–patient relationship is a central factor in delivering high-quality health care, because the patient needs sureness in the competence of the doctor (Mahmud, 2009).

Informal caregivers such as family and friends have been found to improve MAA among HIV-positive patients (Johnson et al., 2003; Knowlton et al., 2007; Power et al., 2003; Remien et al., 2003). This occurs because informal caregivers can provide social support. A meta-analysis of 122 studies revealed that social support has the strongest relationship with ART adherence (DiMatteo, 2004). Moreover, informal caregivers can remind patients to take medications and can plan follow-up medical appointments (Mosack & Petroll, 2009). What is less known is the influence of caregiver trust from formal caregivers on MAA. Emotional support from a formal caregiver includes three dimensions: (1) informational support refers to help with both seeking and understanding medical information; (2) decision-making support refers to assistance in medical decisions which have to be made; (3) emotional support refers to empathy, reassurance, love and caring (Arora, Finney Rutten, Gustafson, Moser & Hawkins, 2007). Previous research into the helpfulness of emotional support received from the caregiver for breast cancer patients showed that 84% of the patients got very helpful support in information seeking and understanding. From support with decision making it was 75.2% and from emotional support it was 67.1% (Arora et al., 2007). The purpose of this study, then, is to examine to what extent (formal) caregiver trust is influencing MAA.

*In the context of rural South Africa: distance to clinic (DTC) and health literacy*

Besides those variables, two variables which represent the context of rural South Africa are taken into account. Many HIV infected people have difficulties with going to their medical appointment and getting the treatment (Weiser et al., 2003). As a result of stigma, most people living with HIV in Southern Africa have disclosed their status to their relatives and choose a clinic far away from home (Greeff et al, 2008; Skinner & Mfecane, 2004). Transportation costs can be an important barrier for MAA in rural South Africa due to the high level of unemployment and the low income (Siedner et al., 2013; Statistics South Africa, 2017).

Therefore, in the current research we investigated whether distance to clinic is a moderator between caregiver trust and MAA.

Health literacy measures in which extent the patient understands basic health information the caregiver provides them which they need to make appropriate health decisions (Parker, 2000). Earlier research has shown a negative relationship between low health literacy and health outcomes (Berkman, Sheridan, Donahue, Halpern, & Crotty, 2011) and with low health literacy and ART adherence (Kalichman et al., 2008). The access to school in rural South Africa is much lower than in wealthier parts of the country. Moreover, many patients in rural South Africa do not have access to internet and cannot read or write. This implies that lack of health literacy could occur more often in rural South Africa than in the wealthier parts of county. It also happens that the caregiver and patient do not speak the same language due to the 11 official spoken languages in South Africa (Schlemmer & Mash, 2006). Earlier research showed that people living with poor literacy living with HIV were more likely to miss treatment doses for a variety of reasons such as confusion, depression and desire to cleanse their body than people with higher health literacy living with HIV (Kalichman, Ramachandran & Catz, 1999; Kalichman et al., 2008; Osborn Davis, Bailey & Wolf, 2010; Waite, Paasche-Orlow, Rintamaki, Davis & Wolf, 2008; Waldrop-Valverde et al., 2010). Additionally, people with poor literacy are more likely to misunderstand medication instructions, which can lead to missed doses or overdosing (Wolf et al., 2007). This study investigates whether the level of health literacy explains the relationship between caregiver trust and MAA.

**This study**

A variety of medical studies have already been conducted regarding treatment options for HIV and AIDS (Bhatti, Usman & Kandi, 2016; Hammer et al., 2006; Antoniou & Tseng 2005), quality of life with ART (Mafirakureva, Dzingirai, Postma, Van Hulst & Khoza, 2016; Yahaya, Olorukooba, Yusuf, Abdulrahman & Amadu, 2016; Yang, Thai & Choi, 2016) and barriers for ART adherence (Field, 2015; Saberi et al., 2015; Hudelson & Cluver, 2015; Viswanathan et al., 2015). Unfortunately, there are still many patients dying from HIV and AIDS, even when they have access to ART (UNAIDS, 2018). Overall treatment success relies on ART adherence. Therefore, we examine caregiver trust as social and behavioural factor that may influence MAA, because we know from previous research that MAA has a positive influence on ART adherence.

The main research question is *What is the association between caregiver trust and MAA, and how are health literacy and DTC related to caregiver trust and MAA in rural South Africa?* The following sub questions are made to answer the main research question: (1) *What is the association between caregiver trust and MAA in rural South Africa?*; (2) *Does DTC strengthen the effect between caregiver trust and MAA?* and (3) *How is health literacy related to caregiver trust and MAA in rural South Africa?*

*Hypotheses*

After studying the relevant literature, the following three hypotheses are made:

1. Caregiver trust has a positive association with MAA in rural South Africa.
2. DTC strengthens the association between caregiver trust and MAA.
3. Health literacy is a mediator between caregiver trust and MAA.

The hypotheses are visualized in figure 1.

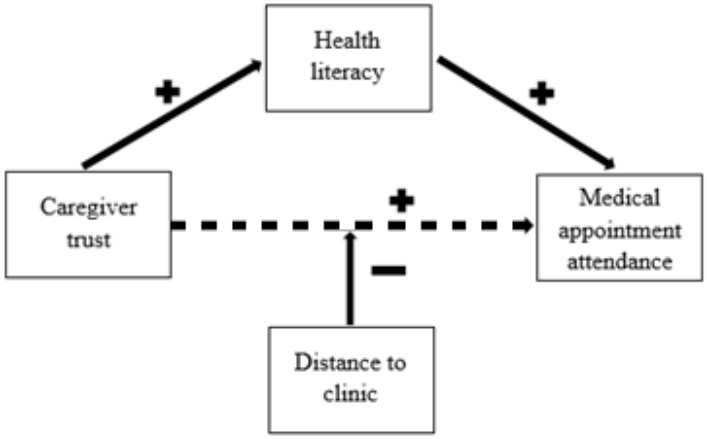


Figure 1: conceptual model hypothesis

**Methods**

*Participants*

All variables are measured through existing data from the Intensified Treatment Monitoring Accumulation (ITREMA) baseline questionnaire and through patient information from their patient file. ITREMA is a randomized control trial that investigated intensified treatment monitoring for HIV patients in rural South Africa (Wensing, 2018). The participants of the ITREMA trial were recruited during their medical appointments at Ndlovu Medical Centre; an HIV and AIDS clinic in Elandsdoorn, Limpopo, rural South Africa. HIV patients were eligible to participate in the ITREMA trial if they were at least 18 years old and getting ART or were about to start ART. Five-hundred-and-one eligible patients agreed to participate in the ITREMA trial. Of the 501 patients, 208 participants has just began ART, and the remaining 293 participants had already been using ART for a longer time period. Participants of the research did not come to the clinic for the research only, but always in combination with their medical appointment. The healthcare was for free. Public transportation to the clinic was available, but at their own cost.

*Procedure*

At study entry, all the participants completed the baseline questionnaire. Participants were enrolled between June 2015 and August 2017. Participants were assisted by counsellors who spoke their languages. This was necessary because most participants had limited literacy skills. The baseline questionnaire contained questions regarding demographics, illness, lifestyle, weight measurements, blood tests, alcohol use and current intake of any medications. The baseline questions that are specifically applicable to this study are those concerning caregiver trust and health literacy. The data for MAA and DTC were collected for this study at the Ndlovu Medical Centre and were not part of the baseline questionnaire.

*Measurements*

*Medical Appointment Attendance (MAA)*

MAA was assessed on patient files by sifting through all the patient files to ascertain how each was doing with their clinical visits. The data are then added to the data file of the ITREMA trial. MAA is scored as a dichotomous variable with the options: the patient is in care and attends the medical appointments (score = 1) or does not attend the medical appointments and is lost to follow-up (LTFU) (score = 0) and stayed away of the clinic for at least 90 days after their last scheduled medical appointment.

*Caregiver trust*

Caregiver trust is measured with 'The Helping Alliance Questionnaire' (HAQ-2) (Luborsky et al., 1996). This standardized questionnaire of 19 items evaluates the relationship between a patient and his/her caregiver and whether the patient trusts the caregiver. Eleven of those questions focus on the trust in the caregiver whilst the remainder are more focused on trust in the caregiver as a psychotherapist due to the focus of the questionnaire's initial creation (Luborsky et al., 1996). The baseline questionnaire of ITREMA trial is using the 11 questions in the baseline questionnaire with focus on the patient's trust and relationship with the caregiver at Ndlovu Medical Centre. Examples of questions are: '*a good relationship has formed with my clinician*' or '*I feel the clinician understands me.*' The responses are measured on a six-point Likert scale, from 'strongly disagree' to 'strongly agree'. A higher score represents more trust in the caregiver. The Cronbach's Alfa of the HAQ-2 = .82 (This is based on the 11 items of the ITREMA baseline questionnaire). The Cronbach's Alfa does not get higher if one item is deleted.

*Distance to Clinic (DTC)*

Data about DTC is based on analysis on Google Maps between the patient's residence and the clinic. First, all the addresses of the patients were collected from the patient files. Second, their home villages are added in Google Maps. The distance is not measured by their street, but at the central point of their village to the clinic in kilometres. The distance is measured over roads and not as the crow flies. This data is added to the ITREMA baseline questionnaire dataset.

*Health literacy*

Health literacy is measured with the Brief Estimate of Health Knowledge and Action (BEHKA)-HIV Version (Osborn et al., 2008). This questionnaire is measuring the amount of HIV treatment knowledge and action. Four questions are measuring the theoretical health knowledge of HIV and five questions are measuring operational knowledge. An example of a question in the theoretical part of the questionnaire is '*What is CD4-count?*' The answers of participants were checked with the guidelines of the BEHKA-HIV. The Cronbach's Alfa of the theoretical questions of the BEHKA-HIV = .36. The Cronbach's Alfa is very low, but this is because the scale is not unidimensional. This questions only had open and dichotomous questions which can assume a huge variance in answers. There is no assumption that these questions should give homogenous answers.

The operational knowledge is measured by five questions which are measured on a three-point Likert scale with the options agree, unsure and disagree. An example of the operational knowledge part of the questionnaire is '*I don't take my ARV's when they make me feel bad*'. The Cronbach's Alfa of the operational questions of the BEHKA-HIV = .84.

Based on the BEHKA-HIV, participants could score between 1 and 7; two points for the theoretical knowledge and 5 points for the operational knowledge. Health literacy is categorized in three categories: low, middle and high health literacy. All participants were people with HIV and the measured knowledge is very basic for a HIV patient to know. That is why the scores 1 till 5 are considered as low health literacy, a score of 6 as middle health literacy and a score of 7 as high health literacy.

*Control variables*

There might be other factors that influence the MAA rate besides those independent variables described. To correct for these factors, we have taken control variables into account. The control variables are gender, age, level of education and income. To measure gender,

participants were asked if they were a man (score = 0) or a woman (score = 1). Regarding age, the date of birth was asked. For the analyses, the date of birth was then computed into years in age. Moreover, the level of education was asked. The school system in South Africa represents grades 1 – 14. In this research, level of education was categorized as low, middle and high. Low education represents grades 1 – 7 which is primary school. Middle education represents grades 8 – 12 which is high school and college. High education represents grades 13 – 14 which is university. The amount of income per month was asked as an open-end question. Afterwards the variable is changed as a dichotomous variable with the options no income (score = 0) and having income (score = 1).

*Statistical analyses*

Statistical Package for the Social Sciences (SPSS) version for Windows was utilised for the statistical analyses. First, sample size characteristics and descriptions of the study variables are given. Univariate analyses with logistic regression are used to see the association between the control and independent variables. After, multiple logistic regression is used to ascertain the association between caregiver trust and MAA when the mediator, moderator and control variables are included in the model.

Hayes' (2017) PROCESS macro model 5 in SPSS was used to analyse if DTC moderates the association between caregiver trust and MAA, and to analyse if health literacy mediates the association between caregiver trust and MAA. Moderation means that a third variable affects the direction or strengthen the relation between the independent and dependent variable. Moderation is analysed with the interaction effect of caregiver trust * DTC. Mediation means that the relationship between caregiver trust and MAA goes through health literacy. Mediation is analysed through the following steps: (1) measure if there is an association between caregiver trust on health literacy, (2) measure if there is an association between health literacy and MAA and (3) measure if there is still a relationship between caregiver trust and MAA with taking health literacy into account. There is mediation if step one and two are significant and step three is not significant. There is partial mediation if step one and two are significant, but step three stays also significant. There is no mediation if step one and/or two is not significant.

**Results**

*Sample characteristics*

Descriptive statistics were computed for all study variables. The sample characteristics are shown in Table 1.

Table 1.

*Descriptive statistics for the sample of ITREMA trial (N = 501)*

| | Frequency | Percentage | Mean | SD | Range |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 150 | 29.9 | | | |
| Female | 351 | 70.1 | | | |
| Age | | | 42.65 | 10.33 | 18 - 72 |
| Level of education | | | | | |
| Low | 93 | 18.6 | | | |
| Middle | 377 | 75.2 | | | |
| High | 31 | 6.2 | | | |
| Income | | | 3497.57 | 5561.31 | 0 – 80.000 |
| No income | 260 | 51.9 | | | |
| Having income | 241 | 48.1 | | | |
| Medical appointment attendance | | | | | |
| In care | 422 | 84.4 | | | |
| Lost to follow-up | 78 | 15.6 | | | |
| Caregiver trust | | | 5.47 | .48 | 3.5 – 6.0 |
| Distance to clinic | | | 38.37 | 34.35 | 1 - 181 |
| ≤ 30 kilometres | 234 | 46.7 | | | |
| >30 kilometres | 267 | 53.3 | | | |
| Health literacy | | | | | |
| Low health literacy | 52 | 10.5 | | | |
| Middle health literacy | 118 | 23.9 | | | |
| High health literacy | 323 | 65.5 | | | |

The sample included 150 (29.9%) men and 351 (70.1%) women. This reflects the HIV epidemic in South Africa; HIV prevalence among young women in South Africa is nearly

four times greater than men of the same age (South African National AIDS Council, 2017). The average age was 42.65 year (SD = 10.33). The youngest participant was 18 and the oldest 71. Ninety-three (18.6%) participants are considered as low educated, 377 (75.2%) as medium educated and 31 (6.2%) as high educated. Two-hundred-and-sixty participants did not have any income and 241 participants did. The average income was 3497.57 South African Rand per month (SD = 5561.31), this is approximately 235 euro per month. The minimum income was 0 and the maximum income 80.000 South African Rand per month. Sixty (12%) participants said that they did not have enough money for food at least once in the last 12 months.

Four-hundred-twenty-two (84.4%) participants were still in care and 78 (15.6%) participants were out of care. There were no missing values in the variable MAA. The lowest score on caregiver trust was 3.5 and the highest 6.0. The mean was 5.47 (SD = .48). There were 6 missing values for caregiver trust. Two-hundred-thirty-two (46.7%) participants lived 30 kilometres or closer from the clinic and 267 (53.3%) participants lived further than 30 kilometres away from the clinic. The closest participant lived one kilometre away from the clinic and the most distant 181. The average distance to clinic was 38.37 km (SD = 34.35). There were no missing values for distance to clinic (DTC). The scores at health literacy ranged between 1 and 7, with a mean of 6.51 (SD = .83). Fifty-two participants (10.5%) scored low on health literacy, 118 participants (23.9%) medium and 323 participants (65.5%) high. There were 8 missing values for health literacy.

*Associations with medical appointment attendance*

Assumptions of logistic regression are evaluated before starting the analyses. None of the evaluated assumptions were violated. The dependent variable is binary, observations did not come from repeated measurements and there was no multicollinearity between the factors (VIF = <10).

Univariate analyses with logistic regression were performed to examine the associations with MAA (Table 2). Of the control variables, gender and age were significantly associated with MAA, more specified are men associated with a lower MAA then women. Among men, 22.0% became out of care and among women 12.8%. Level of education and income were not significantly associated with MAA. Of the experimental variables was caregiver trust significantly related to MAA. More trust in the caregiver is associated with a better attendance to medical appointments, as hypothesised. DTC was not associated with MAA, which was also hypothesised. Health literacy was also not associated with MAA which

should not follow the hypothesis, because the expectation is that health literacy is a mediator. PROCESS in SPSS is used to check if health literacy is a mediator between caregiver trust and MAA.

Multivariate logistic regression analyses were next presumed to examine independent associations with MAA. Control variables that were not significant on univariate analyses were not included with multivariate analyses. Gender and age were significant at the multivariate analysis which means that men and people with a younger age have a lower MAA. The association with caregiver trust was also significant as was the association with health literacy. This means that patients with more caregiver trust and health literacy better adhere to medical appointments.

Table 2

*Odds ratio and 95% confidence interval associated with medical appointment attendance; univariate and multivariate analyses*

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | | 95% CI | | | 95% CI | |
| | Odds ratio | Lower | Upper | Odds ratio | Lower | Upper |
| Gender | 1.92* | 1.17 | 3.15 | 2.02* | 1.14 | 3.61 |
| Age | 1.09*** | 1.06 | 1.12 | 1.08*** | 1.05 | 1.11 |
| Level of education | | | | | | |
| 1 | .54 | .26 | 1.14 | | | |
| 2 | .37 | .124. | 1.09 | | | |
| Income | 1.17 | .718 | 1.90 | | | |
| Caregiver trust | 2.84*** | 1.70 | 4.76 | 2.39** | 1.30 | 4.41 |
| Distance to clinic | 1.40 | .87 | 2.28 | 1.41 | .82 | 2.43 |
| Health literacy | | | | | | |
| 1 | 2.89 | 1.33 | 6.26 | 2.45* | 1.02 | 5.88 |
| 2 | 3.44 | 1.76 | 6.70 | 2.45* | 1.16 | 5.17 |

* P < .05

** P < .01

*** P < .001

Note: gender: 1 = male, 2 = female (male is reference category), level of education: 1 = medium, 2 = high (low is reverence category), health literacy: 1 = medium, 2 = high, (low is reference category).

*Output PROCESS interaction caregiver trust and DTC*

DTC was not a significant moderator of the association between caregiver trust and MAA; there was no significant interaction between caregiver trust * DTC. This means that DTC is not strengthen the relation between caregiver trust and MAA. This is shown in Table 3.

Table 3

*Process of Hayes for the interaction of distance to clinic and caregiver trust*

| | | 95% CI | |
|---|---|---|---|
| | Coefficient | Lower | Upper |
| Gender | .80* | .24 | 1.35 |
| Age | .08*** | .05 | .11 |
| Caregiver trust | .86** | .31 | 1.41 |
| DTC | .39 | -.17 | .95 |
| caregiver trust * DTC | .62 | -.48 | 1.72 |

* P < .05

** P < .01

*** P < .001

*Output PROCESS to measure health literacy as mediator*

Three sets of output given by PROCESS are used to determine whether health literacy mediates the relationship between caregiver trust and MAA. The first output measured the direct effect; if there is a relationship between caregiver trust and MAA. This relationship is already made in the analyses with logistic regression and is significant. Second, the relation between caregiver trust and health literacy and the relationship between health literacy and MAA is measured. This is the indirect effect. The relationship between caregiver trust and health literacy is measured significant (P = < .001). Gender and age are insignificant in the relationship between caregiver trust and health literacy. The relationship between health literacy and MAA was also significant (p = .04). Caregiver trust stays also significant (p = .01) and gender and age are also significant. Lastly, the direct effect between caregiver trust and MAA is measured with taking health literacy into account and the indirect effect between health literacy, caregiver trust and MAA. The direct effect stayed significant (p = .01) while the indirect effect was no longer. This means that health literacy is a partial mediator between caregiver trust and MAA. Partial meaning the path from caregiver trust to MAA is reduced by health literacy, but still significant. The output is shown in Table 4.

Table 4

*Regression analyses with process for health literacy and medical appointment attendance*

| | | 95% Confidence interval | | | 95% Confidence interval | |
|---|---|---|---|---|---|---|
| | Coefficient | Lower | Upper | Coefficient | Lower | Upper |
| Gender | .12 | -.01 | .24 | .77** | .22 | 1.33 |
| Age | -.00 | -.01 | .00 | .08*** | .05 | .11 |
| Caregiver trust | .45*** | .33 | .57 | .74* | .15 | 1.32 |
| Health literacy | | | | .39* | .02 | .75 |

* P < .05

** P < .01

*** P < .001

**Discussion**

This study intends to identify factors which are associated with medical appointment attendance (MAA) of people living with HIV in the setting of rural South Africa. This study shows that caregiver trust is positively associated with MAA in this area. Of the other factors investigated, gender and age are influencing MAA. Specifically, men, younger people and people with lower trust in the caregiver are associated with lower MAA. These are important findings since the current lost to follow-up (LTFU) rate in the ITREMA trial is 15.6%.

The distance to the clinic does not strengthen the effect between caregiver trust and MAA, because the interaction between caregiver trust and DTC is not significant. This means that the second hypothesis is not supported. Health literacy is a partial mediator between caregiver trust and MAA, thus the path from caregiver trust to MAA is reduced by health literacy, but still significant. The paths between caregiver trust and health literacy and between health literacy and MAA are also significant. This supports the last hypothesis of this study.

There are no other studies found focussing on the association between caregiver trust and MAA in rural areas, but it has been shown that support from informal caregivers are positively associated with better ART adherence and better MAA (Johnson et al., 2003; Knowlton et al., 2007; Power et al., 2003; Remien et al., 2003). Besides, caregiver trust is a form of formal social support, which is in other studies also associated with better MAA (Gonzalez et al., 2004; Catz et al., 2000; Catz et al., 1999).

Other studies found mixed results in gender as predictor of MAA. A study in the rural area of Rwanda also found that men have less MAA (Rich et al., 2012), while Catz et al. (1999) no difference found in gender and Giordano et al. (2009) found that men who are having sex with men better adhere to MAA in the United States (Giordano, Hartman, Gifford, Backus & Morgan 2009). A younger age was in other studies also associated with less MAA (Catz et al., 1999; Giordano et al., 2009; Boyles, Wilkinson, Leisegang & Maartens, 2011), but a study in Rwanda found an association of people older than 50 years with lower MAA (Rich et al., 2012). Income and level of education was in other studies not associated with lower MAA (Catz et al., 1999).

Limitations are important to take into account while interpreting the results of this study. There is a constraint of content validity for the measurements of DTC and health literacy. DTC is measured by the distance from the house to the clinic, but a large percentage of people in South Africa have two residences. Families usually have two houses, one for the weekends and one for during the working week. The medical appointments in the clinic can only be made for weekdays which suggest that people chose a clinic close to their work where they can go during weekdays instead of a clinic close to their home address. Besides, this study anticipates a greater distance with poorer MAA, but it can also suggest greater MAA, because people with a greater distance might chose this clinic for a specific reason. Other elements in the context of South Africa need to be taken into account to see the impact of DTC correctly, such as employment, distance from work to clinic and reason for attending this clinic. A second limitation is the instrument by which health literacy is measured. The questions used for health literacy was initially made for the medical sciences and include mainly questions about if the patient understands the sickness and less about how the patient understands the caregiver. A more social science questionnaire should include more questions about if the patient has the feeling of understanding the caregiver, instead of asking questions about the sickness itself.

Another important limitation of the results of this study is in which degree findings are generalizable to whole rural South Africa. There is limited data on MAA, especially in rural areas. More data in the same settings are required to enable the results of different studies to be able to generalize the results. This indicates directly the strength of this study: the sample of patients used for this study is very relevant for this research area, and as such, should be extended into other rural areas in South Africa to see if they get similar results. There is need for more research about caregiver trust as a predictor to enable an increase in MAA in the rural setting. Further research is also needed to explain how DTC is related to caregiver trust

and MAA. Finally, this research should be repeated with another measurement for health literacy.

Since an increasing number of people living with HIV are using antiretroviral therapy (ART), long-term care is becoming more important. MAA is likely to be an important determinant of health outcomes due to its relationship with ART adherence. This study suggests that special attention is needed for MAA for men and young people living with HIV. Caregivers may need to put more effort into helping people who are having difficulties with adhering to their appointments. Finally, since more caregiver trust is associated with better MAA, interventions targeting greater caregiver trust are likely to be effective for MAA. Suggestions for interventions are that the caregivers need to always speak the same language as the patient and that there should be at least 10 minutes available for each appointment.

In summary, the success of ART in rural South Africa is threatened by poor MAA. This study shows that lower LTFU rates are achievable, even in rural areas, by focusing on caregiver trust, men and younger people. Interventions regarding better caregiver trust and programs regarding men and younger people may be able to improve MAA. Further research is needed to better understand how caregiver trust and other factors are influencing MAA.

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**Reference list**

Antoniou, T., & Tseng, A. L. (2005). Interactions between antiretrovirals and antineoplastic drug therapy. *Clinical pharmacokinetics*, *44*(2), 111-145.

Arora, N. K., Finney Rutten, L. J., Gustafson, D. H., Moser, R., & Hawkins, R. P. (2007). Perceived helpfulness and impact of social support provided by family, friends, and health care providers to women newly diagnosed with breast cancer. Psycho-Oncology, 16(5), 474-486.

Berkman, N. D., Sheridan, S. L., Donahue, K. E., Halpern, D. J., & Crotty, K. (2011). Low health literacy and health outcomes: an updated systematic review. Annals of internal medicine, 155(2), 97-107.

Bhatti, A. B., Usman, M., & Kandi, V. (2016). Current scenario of HIV/AIDS, treatment options, and major challenges with compliance to antiretroviral therapy. Cureus, 8(3).

Boyles, T. H., Wilkinson, L. S., Leisegang, R., & Maartens, G. (2011). Factors influencing retention in care after starting antiretroviral therapy in a rural South African programme. PloS one, 6(5), e19201.

Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & McAuliffe, T. L. (2000). Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. Health Psychology, 19, 124–133.

Catz, S. L., McClure, J. B., Jones, G. N., & Brantley, P. J. (1999). Predictors of outpatient medical appointment attendance among persons with HIV. AIDS Care, 11, 361–373.

Ciechanowski, P. S., Katon, W. J., Russo, J. E., & Walker, E. A. (2001). The patient-provider relationship: attachment theory and adherence to treatment in diabetes. American Journal of Psychiatry, 158(1), 29-35.

Clayson, D.J., Wild, D.J., Quarterman, P., Duprat-Lomon, I., Kubin, M., & Coons, S.J. (2006). A comparative review of health-related quality-of-life measures for use in HIV/AIDS clinical trials. PharmacoEconomics, 24(8), 751—765.

Crum, N. F., Riffenburgh, R. H., Wegner, S., Agan, B. K., Tasker, S. A., Spooner, K. M., ... & Triservice AIDS Clinical Consortium. (2006). Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. JAIDS Journal of Acquired Immune Deficiency Syndromes, 41(2), 194-200.

Cruz M, Pincus HA (2002) Research on the influence that communication in psychiatric encounters has on treatment. Psychiatr Serv 53(10):1253–1265.

Deeken, J. F., Pantanowitz, L., & Dezube, B. J. (2009). Targeted therapies to treat Non-AIDS Defining Cancers in patients with HIV on HAART therapy–treatment considerations and research outlook. *Current opinion in oncology*, *21*(5), 445.

DiMatteo, M. R. (2004). Social support and patient adherence to medical treatment: a meta-analysis. Health psychology, 23(2), 207.

Field, T. (2015). Barriers to Antiretroviral Therapy Adherence: Descriptive literature review.

Giordano, T. P., Hartman, C., Gifford, A. L., Backus, L. I., & Morgan, R. O. (2009). Predictors of retention in HIV care among a national cohort of US veterans. HIV clinical trials, 10(5), 299-305.

Gonzalez, J. S., Penedo, F. J., Antoni, M. H., Durán, R. E., McPherson-Baker, S., Ironson, G., ... & Schneiderman, N. (2004). Social support, positive states of mind, and HIV treatment adherence in men and women living with HIV/AIDS. Health Psychology, 23(4), 413.

Greeff, M., Phetlhu, R., Makoae, L. N., Dlamini, P. S., Holzemer, W. L., Naidoo, J. R., ... & Chirwa, M. L. (2008). Disclosure of HIV status: experiences and perceptions of persons living with HIV/AIDS and nurses involved in their care in Africa. Qualitative health research, 18(3), 311-324.

Hammer, S. M., Saag, M. S., Schechter, M., Montaner, J. S., Schooley, R. T., Jacobsen, D. M., ... & Gatell, J. M. (2006). Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society–USA panel. *Jama*, *296*(7), 827-843.

Hayes, A. F. (2017). Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. Guilford Publications.

Healthline. (2016). Everything You Need to Know About HIV/AIDS. (2018, February 8). Retrieved from https://www.healthline.com/health/hiv-aids?ref=global#modal-close.

Hill, S., & Kavookjian, J. (2012). Motivational interviewing as a behavioral intervention to increase HAART adherence in patients who are HIV-positive: a systematic review of the literature. AIDS care, 24(5), 583-592.

Hudelson, C., & Cluver, L. (2015). Factors associated with adherence to antiretroviral therapy among adolescents living with HIV/AIDS in low-and middle-income countries: a systematic review. AIDS care, 27(7), 805-816.

Hugtenburg, J. G., Timmers, L., Elders, P. J., Vervloet, M., & van Dijk, L. (2013). Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. Patient preference and adherence, 7, 675.

Johnson, M. O., Catz, S. L., Remien, R. H., Rotheram-Borus, M. J., Morin, S. F., Charlebois, E., ... & Chesney, M. A. (2003). Theory-guided, empirically supported avenues for intervention on HIV medication nonadherence: findings from the Healthy Living Project. AIDS Patient care and STDS, 17(12), 645-656.

Kalichman, S. C., Pope, H., White, D., Cherry, C., Amaral, C. M., Swetzes, C., ... & Kalichman, M. O. (2008). Association between health literacy and HIV treatment adherence: further evidence from objectively measured medication adherence. Journal of the International Association of Physicians in AIDS Care, 7(6), 317-323.

Kalichman, S. C., Ramachandran, B., & Catz, S. (1999). Adherence to combination antiretroviral therapies in HIV patients of low health literacy. Journal of general internal medicine, 14(5), 267-273.

Klatt, E. C. (2016). PATHOLOGY OF HIV/AIDS. Atherosclerosis". Utah. Edu.

Knowlton, A. R., Arnsten, J. H., Gourevitch, M. N., Eldred, L., Wilkinson, J. D., Rose, C. D., ... & INSPIRE Study Team. (2007). Microsocial environmental influences on highly active antiretroviral therapy outcomes among active injection drug users: The role of informal caregiving and household factors. JAIDS Journal of Acquired Immune Deficiency Syndromes, 46, S110-S119.

Kravitz, R. L., & Melnikow, J. (2004). Medical adherence research: time for a change in direction?.

Krummenacher, I., Cavassini, M., Bugnon, O., & Schneider, M. P. (2011). An interdisciplinary HIV-adherence program combining motivational interviewing and electronic antiretroviral drug monitoring. AIDS care, 23(5), 550-561.

Lacro, J. P., Dunn, L. B., Dolder, C. R., Leckband, S. G., & Jeste, D. V. (2002). Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. The Journal of clinical psychiatry.

Luborsky, L., Barber, J. P., Siqueland, L., Johnson, S., Najavits, L. M., Frank, A., & Daley, D. (1996). The revised helping alliance questionnaire (HAq-II): psychometric properties. The Journal of psychotherapy practice and research, 5(3), 260.

Mafirakureva, N., Dzingirai, B., Postma, M. J., Van Hulst, M., & Khoza, S. (2016). Health-related quality of life in HIV/AIDS patients on antiretroviral therapy at a tertiary care facility in Zimbabwe. AIDS care, 28(7), 904-912.

Mahmud, A. (2009). Doctor-patient relationship. Pulse, 3(1), 12-14.

Maurice, J. (2014). South Africas battle against HIV/AIDS gains momentum. Lancet, 383(9928), 1535-6.

McDonald, H. P., Garg, A. X., & Haynes, R. B. (2002). Interventions to enhance patient adherence to medication prescriptions: scientific review. Jama, 288(22), 2868-2879.

Montaner, J. S., Reiss, P., Cooper, D., Vella, S., Harris, M., & Conway, B. et al. (1998). A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: The INCAS Trial. Italy, the Netherlands, Canada and Australia Study. Journal of the American Medical Association, 279, 930–937.

Mosack, K. E., & Petroll, A. (2009). Patients' perspectives on informal caregiver involvement in HIV health care appointments. AIDS patient care and STDs, 23(12), 1043-1051.

Osborn, C. Y., Davis, T. C., Bailey, S. C., & Wolf, M. S. (2010). Health literacy in the context of HIV treatment: introducing the Brief Estimate of Health Knowledge and Action (BEHKA)—HIV version. AIDS and Behavior, 14(1), 181-188.

Parker, R. (2000). Health literacy: a challenge for American patients and their health care providers. Health Promotion International, 15(4), 277-283.

Power, R., Koopman, C., Volk, J., Israelski, D. M., Stone, L., Chesney, M. A., & Spiegel, D. (2003). Social support, substance use, and denial in relationship to antiretroviral treatment adherence among HIV-infected persons. AIDS patient care and STDs, 17(5), 245-252.

Remien, R. H., Hirky, A. E., Johnson, M. O., Weinhardt, L. S., Whittier, D., & Le, G. M. (2003). Adherence to medication treatment: A qualitative study of facilitators and barriers among a diverse sample of HIV+ men and women in four US cities. AIDS and Behavior, 7(1), 61-72.

Rich, M. L., Miller, A. C., Niyigena, P., Franke, M. F., Niyonzima, J. B., Socci, A., ... & Epino, H. (2012). Excellent clinical outcomes and high retention in care among adults in a community-based HIV treatment program in rural Rwanda. JAIDS Journal of Acquired Immune Deficiency Syndromes, 59(3), e35-e42.

Saberi, P., Neilands, T. B., Vittinghoff, E., Johnson, M. O., Chesney, M., & Cohn, S. E. (2015). Barriers to antiretroviral therapy adherence and plasma HIV RNA suppression among AIDS clinical trials group study participants. AIDS patient care and STDs, 29(3), 111-116.

Schlemmer, A., & Mash, B. (2006). The effects of a language barrier in a South African district hospital. South African Medical Journal, 96(10), 1084-1087.

Shepherd, B. E., Blevins, M., Vaz, L. M., Moon, T. D., Kipp, A. M., José, E., ... & Vermund, S. H. (2013). Impact of definitions of loss to follow-up on estimates of retention, disease progression, and mortality: application to an HIV program in Mozambique. American journal of epidemiology, 178(5), 819-828.

Shisana, O., Rehle, T., Simbayi, L.C., Parker, W., Zuma, K., Bhana, A., Connoly, C., Jooste, S. & Pillay, V. (2005). South African National HIV Prevalence, HIV Incidence, Behavior and Communication Survey, 2005. Cape Town: HSRC Press.

Siedner, M. J., Lankowski, A., Tsai, A. C., Muzoora, C., Martin, J. N., Hunt, P. W., ... & Bangsberg, D. R. (2013). GPS-measured distance to clinic, but not self-reported transportation factors, are associated with missed HIV clinic visits in rural Uganda. AIDS (London, England), 27(9), 1503.

Simoni, J. M., Pearson, C. R., Pantalone, D. W., Marks, G., & Crepaz, N. (2006). Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load: a meta-analytic review of randomized controlled trials. Journal of acquired immune deficiency syndromes (1999), 43(0 1), S23.

Singh, N., Berman, S. M., Swindells, S., Justis, J. C., Mohr, J. A., Squier, C., & Wagener, M. M. (1999). Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. Clinical and Infectious Disease, 29, 824–830.

Skinner, D., & Mfecane, S. (2004). Stigma, discrimination and the implications for people living with HIV/AIDS in South Africa. SAHARA: Journal of Social Aspects of HIV/AIDS Research Alliance, 1(3), 157-164.

South African National AIDS Council (SANAC). (2017). National Strategic Plan for HIV, TB and STIs 2017-2022.

Statistics South Africa (2017). Poverty on the rise in South Africa. (2018, June 1). Retrieved from http://www.statssa.gov.za/?p=10334.

Statistics South Africa. (2018). Statistics South Africa. (2018, February 8). Retrieved from http://www.statssa.gov.za/.

UNAIDS. (2018). HIV and AIDS estimates. (2018, February 8). Retrieved from http://www.unaids.org/en/regionscountries/countries/southafrica.

UNAIDS. (2017). South Africa launches new plan to advance progress towards ending AIDS. (2018, February 8). Retrieved from http://www.unaids.org/en/resources/presscentre/-featurestories/2017/april/20170403_south-africa-NSP.

Viswanathan, S., Justice, A. C., Alexander, G. C., Brown, T. T., Gandhi, N. R., McNicholl, I. R., ... & Jacobson, L. P. (2015). Adherence and HIV RNA suppression in the current Era of Highly Active Antiretroviral Therapy (HAART). Journal of acquired immune deficiency syndromes (1999), 69(4), 493.

Waite, K. R., Paasche-Orlow, M., Rintamaki, L. S., Davis, T. C., & Wolf, M. S. (2008). Literacy, social stigma, and HIV medication adherence. Journal of General Internal Medicine, 23(9), 1367.

Waldrop-Valverde, D., Osborn, C. Y., Rodriguez, A., Rothman, R. L., Kumar, M., & Jones, D. L. (2010). Numeracy skills explain racial differences in HIV medication management. AIDS and Behavior, 14(4), 799-806.

Weiser, S., Wolfe, W., Bangsberg, D., Thior, I., Gilbert, P., Makhema, J., ... & Marlink, R. (2003). Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana. JAIDS-HAGERSTOWN MD-, 34(3), 281-288.

Weiss, K. A., Smith, T. E., Hull, J. W., Piper, A. C., & Huppert, J. D. (2002). Predictors of risk of nonadherence in outpatients with schizophrenia and other psychotic disorders. Schizophrenia bulletin, 28(2), 341.

Wensing, A. (2018). Evaluation of an Intensified Treatment Monitoring Strategy to Prevent Accumulation and Spread of HIV-1 Drug Resistance in Low- and Middle-income Countries (ITREMA). ClinicalTrials.gov Identifier: NCT03357588.

Wolf, M. S., Davis, T. C., Shrank, W., Rapp, D. N., Bass, P. F., Connor, U. M., ... & Parker, R. M. (2007). To err is human: patient misinterpretations of prescription drug label instructions. Patient education and counseling, 67(3), 293-300.

World Health Organization. (2017). HIV/AIDS. (2018, March 16). Retrieved from http://www.who.int/mediacentre/factsheets/fs360/en/.

Worldwide AIDS & HIV Statistics. (2010). AIDS & HIV information from the AIDS charity AVERT. (2018, March 16). Retrieved from http://www.avert.org/worldstats.htm.

Yahaya, S. S., Olorukooba, A. A., Yusuf, R., Abdulrahman, H., & Amadu, L. (2016). Health related quality of life of HIV/AIDS patients on highly active antiretroviral therapy in Ahmadu Bello University Teaching Hospital. International Journal of Infectious Diseases, 45, 271.

Yang, Y., Thai, S., & Choi, J. (2016). An evaluation of quality of life among Cambodian adults living with HIV/AIDS and using antiretroviral therapy: a short report. AIDS care, 28(12), 1546-1550.