**ARCADA**

# Barriers to Antiretroviral Therapy Adherence

Descriptive literature review

Tuuli Field

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Abstract:

Adherence to the treatment regimen is essential to the success of highly active antiretroviral therapy for patients who are infected with HIV. The evidence suggests that poor adherence to antiretroviral drug therapy is a major problem that has the potential to diminish effective viral suppression, promote viral resistance, and place patients at risk for hospitalization, opportunistic infections, and an increased risk of HIV transmission. The primary aim of this study was review was to find and identify current barriers that prevent people from adherence to antiretroviral therapy. The chosen research method was descriptive literature review. Three databases were used for the literature search: CINAHL full text (EBSCO), ProQuest Hospital Collection and Medline (Ovid). Search was limited to articles from years 2010-2015. Articles on children, pregnant women, intravenous drug users, psychiatric patients, post and pre-exposure prophylaxis patients were excluded from the study. After exclusion process 46 articles were accepted for the final analysis. The data was categorized by topics trying to make interpretations from the literature reviewed. Scheduling issues, stigma, adverse side effects and cost were the most commonly found adherence barriers. Scheduling issues and the adverse side effects seem to be universal barriers for patients all over the world. Stigma was more prominent barrier in articles conducted in African countries and cost was found to be a barrier in studies conducted in resource poor settings. High self-efficacy beliefs and social support were the most common positive influences to adherence to ART that rose from the review. The need for new solutions and innovations rose from the results of this review to support patients in scheduling issues nad remembering to take pills in correct time. Furthermore further interventions that effectively target stigma are warranted. Consideration of how healthcare systems and policy can promote and support self-efficacy is required.

| Keywords: | Antiretroviral, adherence, barrier, |
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## FOREWORD

This is the thesis conducted for the Master's Degree Program in Global Health. Antiretroviral therapy (ART) has made HIV a chronic manageable disease. Essential for the success of ART is over 95% adherence rate. After 20 years of antiretroviral therapy several barriers remain to prevent patients to optimal adherence to ART. One afternoon in the Meilahti hospital A&E I had a patient who was dying of HIV related pneumonia, when asked why she had not taken her antiretroviral tablets she answered that the tablets were too big. Her answer got me thinking of the reasons why someone would not commit to a treatment that is lifesaving. Furthermore barriers to adherence still prevent people from reaching 95% adherence rate.

# 1 INTRODUCTION

In June 1981 the Centre for Disease Control and Prevention (CDC) in the US wrote in their weekly report about five previously healthy adult males who had gotten pneumocystis pneumonia (Sutinen, 2012). This was the first indication of a pathogen, which later would be named human immunodeficiency virus (HIV), which would become the most destructive infectious agent in the 20th century (Mandell, 2005, p1655). Due to increasing information and tremendous strides in prevention and treatment in the last ten years, today the life expectancy of a person living with HIV is decades. It has changed from a lethal disease into a chronic condition, with life expectancy being the same of a person cured from cancer (Syrjänen, 2005). This is mostly due to the development of HAART (Highly active antiretroviral therapy), which is a combination drug therapy.

According to the WHO there were 35 million people living with HIV worldwide in the end of 2013. In the year 2013 1.5 million people died of AIDS related illnesses, which is 35% less than in 2005 (WHO, 2015). WHO (2015) estimates that ART (Antiretroviral therapy) programmes averted 7.6 million [6.9 – 8.4 million] deaths between 1995 and 2013. Antiretroviral therapy has dramatic positive effects on the lifespan and quality of life of people living with HIV. Antiretroviral therapy reduces the load of human immunodeficiency virus (HIV) and increases CD4 cell counts, delaying progression to acquired immune deficiency syndrome (AIDS) and reducing morbidity and mortality (Wasti, 2012).

Eradication of HIV infection cannot be achieved with the available antiretroviral (ART) therapy, even when new, potent drugs are added to a regimen that is already suppressing plasma viral load below the limits that can be detected with current lab tests (AIDSinfo, 2015, p. D-1). The antiretroviral therapy is permanent once started (Sutinen, 2012). The patient's adherence to the therapy is essential for its success (Syrjänen, 2005). High level of sustained adherence is necessary to (1) suppress viral replication and improve immunological and clinical outcomes; (2) decrease the risk of developing ARV drug resistance; and (3) reduce the risk of transmitting HIV (WHO, 2013).

In year 2000 the rates of non-adherence to antiretroviral therapy among HIV-positive adults ranged from 37 to 70% (Murphy 2000). Substantial rates of non-adherence have been widely described in the literature despite a multitude of interventions that have been formulated to support and promote high levels of treatment adherence (Sherr, 2008). Ten years later and the adherence levels are not much better. Adherence, for example, in the USA to antiretroviral therapy remains relatively low, most researchers estimate median adherence to be 60-70% (Moitra, 2011). The adherence to the antiretroviral therapy is essential for it success. Understanding factors associated with adherence are critical in order to improve adherence interventions for people living with HIV.

## 2 THEORETICAL FRAME

### 2.1 Antiretroviral therapy

The first medication against the human immunodeficiency virus (HIV) was taken into use in 1987, four years after HIV-1 was identified as the agent that causes AIDS (acquired immunodeficiency syndrome) (Mandell, 2005, p1655). Between the years 1995 and 2003 fifteen new antiretroviral agents were approved for treatment of HIV. These included protease inhibitors, non-nucleoside transcriptase inhibitors (NNRTI's) and a fusion inhibitor (Mandell, 2005, p1655). In mid-1990's a better understanding of the dynamics, replication and drug resistance mechanisms of HIV cased a shift from single to combination drug therapy (Mandell, 2005, 1655). Currently there are over 30 different HIV medications (AIDSinfo, 2015, p A-1). With the advent of highly active antiretroviral therapy (HAART), HIV-1 infection is now manageable as a chronic disease in patients who have access to medication and who achieve durable virologic suppression (Rathbun, 2015).

### 2.2 Highly active antiretroviral therapy (HAART)

The combination drug therapy against HIV is called highly active antiretroviral therapy (HAART). It is most commonly done with the combination of three different medications (Sutinen, 2012). There are currently six different classes of HIV drugs.

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- Protease inhibitors (PIs)

- Integrase inhibitors (INSTIs)

- Fusion inhibitors (FIs)

- Chemokine receptor antagonists (CCR5 antagonists) (Rathbun, 2015)

Each class of drug attacks the virus at different points in its life cycle as the virus infects a $CD4^+$ T lymphocyte or other target cell (Rathbun, 2015). The combination therapy generally includes at least two, and preferably three, different antiretroviral drugs from two or more different drug classes (AIDSinfo, 2015, pA-1). The selection of individual agents for an optimized background regimen should be based on the antiretroviral treatment history, genotypic and/or phenotypic resistance results, drug-drug interaction potential, and medication intolerance, with the goal of maximizing antiviral activity and adherence (Rathbun, 2015). The primary goals for antiretroviral therapy (ART) are to reduce HIV-associated morbidity and prolong the duration and quality of survival, restore and preserve immunologic function, maximally and durably suppress plasma HIV viral load and prevent HIV transmission (AIDSinfo, 2015, p. D-1). Excess mortality among patients with AIDS was nearly halved in the HAART era (see Figure 1.), but it remains approximately 5 times higher in patients with AIDS than in HIV-infected patients without AIDS.
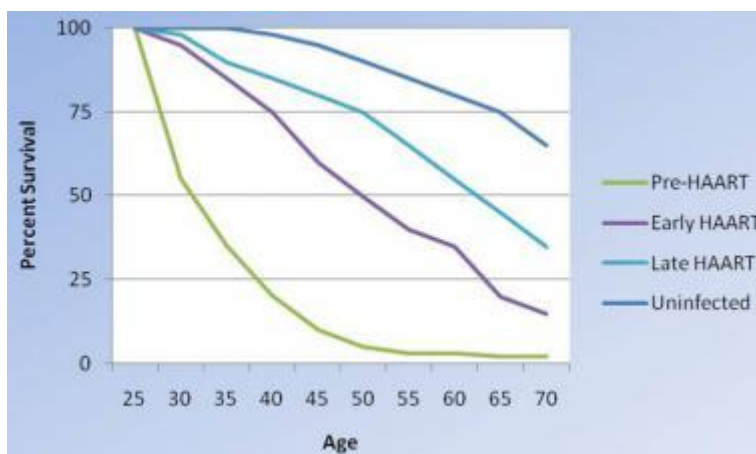


*Figure 1. Changes in survival of people infected with HIV. As therapies have become more aggressive, they have been more effective, although survival with HIV infection is not yet equivalent to that in uninfected people. (Rathbun, 2015)*

The CD4+ cell count thresholds for HAART initiation were recently raised from 350 to 500 cells/mL in the United States and from 200 to 350 cells/mL in mid- and low-income countries (Rathbun, 2015).

Drug resistance is one of the main issues related to HAART. Virus strains with reduced sensitivity to zidovudine, the first drug used to treat HIV infection, were first observed in 1989, three years after it was introduced (Stevens, 2004). Resistance to every currently licensed antiretroviral drug has been observed (Stevens, 2004). Furthermore and they can have serious side effects, such as osteonecrosis and bone demineralization. Protease inhibitor therapy has been associated with hyperlipidemia, hyperglycemia, gastrointestinal symptoms, and body-fat distribution abnormalities (Lesho, 2003). Nonnucleoside reverse transcriptase inhibitors can cause rashes and hepatotoxicity, and nucleoside reverse transcriptase inhibitors can cause lactic acidosis, hypersensitivity reactions, neuropathies, pancreatitis, anemia, and neutropenia. Malabsorption can occur if antiretroviral agents are taken improperly with regard to meals or if they are taken with certain other drugs or herbal remedies (Lesho, 2003). Some commonly prescribed drugs can cause dangerous drug toxicities if they are taken by patients who are also taking certain antiretroviral medications (Lesho, 2003).

## 2.3  Adherence to HAART

According to several studies people do not like taking medications and have often skeptical attitude towards them (Enlund, 2013). It is known that negative or skeptical attitude towards medication is often related to poor adherence (Enlund, 2013). The word adherence is preferred by healthcare providers, instead of words like compliance, as it indicates that the treatment plan is based on alliance or a contract between patient and physician, rather that patient passively following physicians orders (Enholm, 2013; Osterberg, 2005). Medication adherence means taking your HIV medications when and how one is supposed to take them. Average rates for adherence in clinical trials have been found to be high, but rates of adherence for chronic conditions are only found to be 43 to 78% (Osterberg, 2005).

Strict adherence is the key to successful antiretroviral therapy (ART). Optimal adherence to HAART leads to HIV suppression, reduced risk of drug resistance, improved overall health, quality of life, and survival, as well as decreased risk of HIV transmission (AIDSinfo, 2015, p K-1). Patients must take 95 percent of their pills to achieve an 80 percent likelihood of HIV suppression below 50 copies per mL. With less than 95 percent adherence, the probability of suppression to undetectable levels drops to less than 50 percent (Lesho, 2003; Moitra, 2011; Syrjänen, 2005). Failure to take medications regularly and reliably causes the virus to be exposed to suboptimal drug serum concentrations (Lesho, 2003). Non-adherence to ART, may lead to an increase viral load which may lead to drug resistance and loss of future treatment options (Syrjänen, 2005; AIDSinfo, 2015, p K-1). Poor adherence is the major cause of therapeutic failure. Achieving adherence to ART is a critical determinant of long-term outcome in HIV infected patients (AIDSinfo, 2015, pK-1). The adherence for ART is more challenging and more significant than in many other chronic diseases, such as diabetes or hypertension, their drug regimens remain effective even after treatment is resumed after a period of interruption (Syrjänen, 2005; AIDSinfo, 2015, p K-1). This is not the case with HIV.

There is significant amount of research about the reasons behind poor adherence to antiretroviral therapy. Antiretroviral therapies available in the 1990s involved a high pill burden and complex schedule combinations. The efficacy of the treatment was limited as frequent adverse events and the significant interference of treatment in patients' lives made adherence difficult (Fumaz, 2008). In the early days of HAART in 1999 Proctor et al. found the top five barriers to HAART to be frequency and severity of side effects, conflicts with daily routine, dietary requirements, frequency of taking medication, number and dosage of medication. In the present decade advances have been made in HAART such as once-daily regimens have been developed to diminish the negative impact of treatment on quality of life and the appearance of less complex and toxic antiretroviral drugs has improved the management of HIV infection considerably (Fumaz, 2008), but even with the advances made adherence still remains an issue. Adherence is a multidimensional concept that includes contextual, intrapersonal and behavioral factors (Fumaz, 2008). Recent research has found several barriers affecting adherence to ART. These include structural barriers, such as food insecurity or geographic isolation and lack of resources to pay for transportation to clinic (Ketz, 2013). In study done in Botswana

(Weiser, 2003) found that overall economic situation was one of the main barriers, in addition to the cost of the ART, other economic constraints included additional medication expenses, lack of food, lack of money for food and lack of money for clothes for patients and for their children.

As above studies of risk factors in resource-poor settings have focused on access to antiretroviral and food and have shown these to be some of the main barrier for adherence to antiretroviral therapy. In contrast, risk factors for non-adherence in wealthier countries include depression, active drug and alcohol abuse, social instability, and low literacy (AIDSinfo, 2015, pK-1). In a study by Harris et al (2011) it was found that no adherent participants felt less supported by family and perceived having less support for adherence itself. Adherence has been found (Fumaz, 2008) to be related to beliefs about health and illness than to the characteristics of medication or level of knowledge about treatment. Fumaz (2008) found that adherent patients exhibited a higher perception of risk of developing the illness and of the benefits of therapy, higher self-efficacy and intention to adhere and were more influenced by the events that motivate medication intake. Furthermore incorrect beliefs about the medication and dosing, irregular daily schedule, stigma, lack of social support, poor provider-patient relationship, health-care system barriers (such as cost) and medication side effects (Murphy, 2000; Murphy, 2004; Sherr, 2008; Welsh, 2001).

There are many adherence strategies that have been explored, direct observation of all or some doses of antiretroviral therapy is one of them. In a study by Munoz (2011) implemented community-based accompaniment with supervised antiretroviral therapy (CASA) in a resource poor setting and found that it had an impact not only on adherence but also on mortality within the first 2 years, furthermore participants reported greater social support and reduced stigma compared with controls.

## 2.4 Definition of terms

*Adherence*: Someone behaving exactly according to rules, beliefs, etc.: (Cambridge dictionary)

*Adherence to medical regimen*: Extent which patient take medication prescribed by their healthcare provider (Osterberg, 2005)

*Antiretroviral (ARV):* acting, used, or effective against retroviruses (Merriam Webster Dictionary)

*Antiretroviral therapy/treatment (ART):* treatment that suppresses or stops a retrovirus. One of the retrovirus is the human immunodeficiency virus (HIV) that causes AIDS (Medicine.net)

*Barrier*:  a law, rule, problem, etc., that makes something difficult or impossible (Merriam Webster Dictionary)

*Highly active antiretroviral therapy HAART*: combination of protease inhibitors taken with reverse transcriptase inhibitors; used in treating AIDS and HIV (Medicine.net)

## 3   AIM OF THE RESEARCH

The adherence to the antiretroviral therapy is essential for it success. Understanding factors associated with adherence are critical in order to improve adherence interventions for people living with HIV. The purpose of this literature review is to summarize the results of independent studies to determine current knowledge about the barriers to adherence to antiretroviral therapy and draw conclusions that might aid medical professional to support and encourage patients on antiretroviral therapy to adhere. The aim of the research is to find and identify current barriers that prevent people from adherence to antiretroviral therapy. If there are for example cultural, geographical or demographic differences in the level of adherence and barriers to adherence. To answer the question: what are the current barriers that prevent people from adherence to antiretroviral therapy?  Having that knowledge will hopefully help the public health sector in developing new methods of concurring those barriers and to increase the level of adherence which has stayed on the same relatively low level since the ART started.

# 4 RESEARCH METHOD

This research is done as a literature review. The purpose of a literature review is to objectively report the current knowledge on a topic and base this summary on previously published research (Green, 2006, p102). The chosen research method is descriptive literature review or also known as narrative literature review (Kangasniemi, 2013), which is a comprehensive narrative synthesis of previously published information (Green, 2006, p 103). There are many good reasons to write a descriptive overview of literature: they pull many pieces of information together into a readable format, bring practitioners up to date with certain clinical protocols and are helpful in presenting a broad perspective on a topic and often describe development of a problem or its management (Green, 2006).

Kangasniemi (2013) divide the descriptive literature method into four phases: formulation of the research question, selection of the material, synthesise and discussion. Green (2006) includes phase of limitations of the review.

*Setting the research question*: The direction and focus of the descriptive review is defined by the research question (Kangasniemi, 2013). The research question should be explicit and focused so the phenomenon can be examined in debt (Kangasniemi, 2013).

*Sources of information, search terms & delimiting*:  a detailed search of the literature is based upon a focused research question (Green, 2006). The most efficient way to begin a literature search is to use electronic databases (Green 2006, p108; Kangasniemi, 2013) The boundaries set in this step must be comprehensive enough to insure that the author may retrieve all relevant studies, but narrow enough to focus the effort on the relevant articles (Green, 2006, p.108). In this step it is important to briefly describe what selection criteria were used to include or exclude a study from the review (Green, 2006, p108; Kangasniemi, 2013)

*Synthesis*: The information from the literature search is synthesized into evidence tables or comprehensive paragraphs, in order to tease out the differences in the results of different studies (Green, 2006, p.110). Each piece of evidence should be extracted in the same fashion to help decrease the bias of the review (Green, 2006, p109). There is no single

way to write this section. Therefore it is essential to think clearly about what is being conveyed according to the objective of the overview (Green, 2006 , p 110)

*Discussion and limitations*: In this phase the essential findings of the literature review are combined and summarised (Kangasniemi, 2013). Major areas of agreement and disagreement in the literature should be discussed (Green, 2006, p 111). The discussion should tie the study into the current body of literature, provide its clinical significance, and make logical interpretations from the literature reviewed (Green, 2006, p.111). The weaknesses of the review should be addressed and mention areas for improvement (Green, 2006, p, 111).

## 4.1  Literature search

Three databases were used for the literature search: CINAHL full text (EBSCO), ProQuest Hospital Collection and Medline (Ovid). A Boolean search was conducted across all the three databases. Search terms used were antiretroviral therapy and adherence. When using the ProQuest used additionally word barriers. The search included articles published between years 2010 to 2015. Search was limited to articles with full text available online, research done on adults and articles written in English language. Articles on specialized populations as children, pregnant women, intravenous drug users, psychiatric patients and post exposure prophylaxis patients were excluded from the review.

The initial search of these three databases yielded 757 articles (see Figure 2.).  Of which 640 were excluded after screening the titles and abstracts. Articles that were excluded were duplicates or did not appear to contain relevant data on adherence barriers or provided adherence data specific to a specialized population, which were excluded from the study. 117 journal articles were retrieved for full text review. Of these, 71 were excluded on the basis of the criteria for inclusion and exclusion or the full text was not to be found. The final sample included 46 articles (See appendix 1).
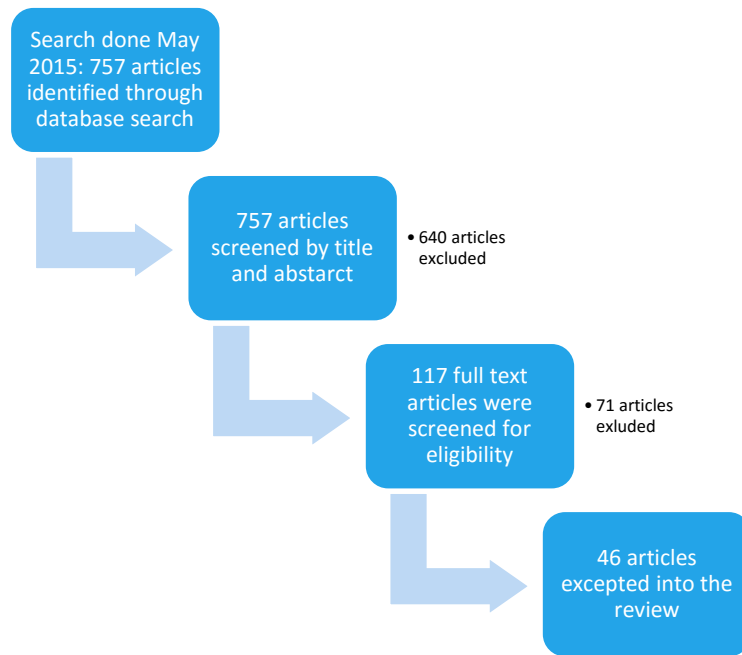
*Figure 2. 757 articles were identified through electronic database search, after exclusion process 46 articles were accepted to the study.*

## 4.2  Analyses

Out of the 757 articles found in the initial search, 46 of those were found relevant to review (see Appendix 1).  Those 46 articles were selected for the final analysis. The articles were read through individually and notes were taken in a form of a data analysis chart (see Appendix 2). Notes taken from each article included the reference, country were the study was conducted, sample, method used, ART adherence percentage, main findings on adherence barriers and comments (see Appendix 2). Comments included factors having positive influence on ART adherence or other findings relevant to the barriers to adherence. The data was categorized by topics trying to make logical interpretations from the literature reviewed.

As each article was read and notes were taken of each article, information retrieved was formulated into paragraphs. The research results found about the barriers to antiretroviral therapy adherence was entered into the data analysis chart. Furthermore research result about positive influences on antiretroviral therapy adherence were entered into the data analysis chart. From the data analysis chart it could be seen that similar themes and barriers were mentioned in several different articles. These barriers were gathered into a table

(see Table 2.) and the number of articles finding the same barriers were counted. As the data analysis chart was analyzed it was clear that several themes arose from the material. The results were divided into five categories: demographic barriers, psychological barriers, regimen related barriers, patient belief related barriers and factors having a positive influence on ART adherence.

## 4.3  Research ethics

In a descriptive review, the findings of existing studies become raw data for analysis and interpretation (Boddy, 1999). One of the most important ethical considerations in a literature review is that it may not always be possible for the reviewer to identify the procedures, for example around consent, that were used to ensure ethical practice in the study being reviewed (Boddy, 1999). I have selected studies that have been peer reviewed and trust that consent was followed in each of the reviewed studies. I assume that the subjects gave permission for activities that were similar in purpose as this review and even if they did not consent specifically to this review. I have done my best to ensure that I treat the work of existing researchers accurately and fairly. I have tried to avoid bias and be systematic in my analysis of the articles selected for the review.

## 5  RESULTS

The results were gathered from 46 articles (See Appendix 1) which were accepted to the final analysis. The articles were published between the years of 2011-2014. The studies varied vastly in method and sample size. Most of the studies were conducted by using a quantitative method, also qualitative and mixed methods were used and one literature reviews. The sample size varied from 27 (Elliot, 2011) to 7034 (Kong, 2012). The studies were conducted around the world. Eighteen of the studies were conducted in different African countries (see Table 1). Of these three studies were conducted in Nigeria (Afolabi, 2013; Okoror, 2013; Oku, 2013), three in South Africa (Magutu, 2011; Nel, 2013; Peltzer, 2010),  two in Tanzania (Lyimo, 2014; Watt, 2010), two in Uganda (Senkomago, 2011; Tuller 2010), one in Egypt (Badahdah, 2011), one in Kenya (Kamau, 2011), one in Democratic Republic of Congo (Musumari, 2013), one in Zambia (Nozaki, 2011) and one in Togo (Potchoo, 2010). Three of the studies had subjects from more than

one country, one from Ethiopia and Uganda (Gustal, 2011), second from Uganda and Zimbabwe (Nyanzi-Wakholi, 2012) and the third was done by using the West Africa, International epidemiological Database (Jaquet, 2010). 13 of the studies were done in the United States (Beer, 2014; Brown, 2013; Colbers, 2013; Kessler, 2011; Kong 2012; Kyser, 2011; Lucey, 2011; King, 2012; Okonsky, 2011; Saberi, 2011; Tyer-Viola, 2014; Vissman, 2013; Wagner, 2012). Six studies conducted in Asia, from which three in China (Fredriksen-Goldsen, 2011; Li, 2012; Li 2011), one in Vietnam (Van Tam, 2011), one is Cambodia (Elliot, 2011) and one in Thailand (Li, 2010). Two the studies were conducted in South America, one in Peru (Curioso, 2010) and one in Brazil (Hanif, 2013), two in Europe, one in Romania (Dima, 2013) and one in Estonia Uuskula, 2012) , and three in India (Saha, 2014; Vallabhaneni, 2012; Venkatesh, 2010) (See Chart 1.). One study was a Strategies for Management of Antiretroviral Therapy (SMART) study. Data from the SMART study were collected in 33 countries on 6 continents (O'Connor, 2013) and one literature review (Al-Dakkak, 2013).

| Africa | 18 |
| --- | --- |
| US | 13 |
| Asia | 6 |
| India | 3 |
| Europe | 2 |
| South America | 2 |

*Table 1. Countries where studies were conducted*

Adherence percentages was given in 28 out of the 46 articles. Most of the given adherence levels, not including three (Colbert, 2013; Maqutu, 2011; Wagner, 2012), were self-reported percentages. Studies conducted in African countries had generally high adherence percentages, average of 84%. Lower percentages were reported in Nigeria (Oku, 2013), Togo (Potchoo, 2010) and South Africa (Maqutu, 2011). Studies done in East African countries of Tanzania (Lyimo, 2014; Watt, 2010) and Kenya (Kamau, 2011) adherence percentages were over 90%. There was eight articles done in the United States which gave the adherence percentage and it was an average of 64%.

### 5.1.1  Demographics

Demographic barriers to adherence were found in twelve different articles. Most commonly found demographic characteristic for poor adherence was black race. It was found in six articles, which were all conducted in The United States (Brown, 2013; Colbert, 2013; Kong, 2012; Kyser, 2011; Saberi, 2011; Wagner, 2013). In a study by Kyser (2011) they found that persons of black race/ethnicity were more than twice as likely to be non-adherent to medications as white persons, which was not explained by employment or education. Kong (2012) found true racial disparity in antiretroviral medication adherence. Being female was found as a barrier in three articles (Hanif, 2013; Beer, 2014; Brown, 2013).  Study done in Brazil (Hanif, 2013) found that women were found to have more severe side effects than men, leading to higher rates of ARV discontinuation among women, furthermore they found that  women experience challenges in accessing ARVs due to lack of knowledge, stigma and discrimination (Hanif, 2013).  Old age was found as a barrier in three articles (King, 2012; O'Connor 2013; Watt, 2010) and young age in four articles (Beer, 2014; Nozaki, 2011; Saha, 2014; Watt, 2010).  Saha (2014) found that patients aged < 30 years were more non-adherent to HAART than patients aged ≥ 30 years.  Watt (2010) found that old age (over 50), to be a barrier, as well as young age (under 30).

### 5.1.2  Regimen related barriers

Most commonly found barriers to ART in the literature were related to the antiretroviral therapy regimen characteristics (See Table 2.). Scheduling, which was found as a barrier in 16 articles, was the commonly found barrier, it includes required time and effort to manage the medication schedule (Curioso, 2010; Dima, 2013; Kamau, 2011; O'Connor, 2013; Oku, 2013), dosing frequency (Beer, 2014; Colbert, 2013; Finocchario-Kessler, 2011; Okonsky, 2011; Vallabhaneni, 2012) or being too busy (Elliot, 2011; Kamau, 2011; Oku, 2013; Saha, 2014; Vallabhaneni, 2012).  Vallabhaneni (2012) found that lack of, or interruption of daily routine, have been cited commonly in studies both in resource-limited settings, and in the developed world as a barrier to adherence.

Furthermore forgetfulness rose as one of the main barriers. It was found in 12 articles (Badahdah, 2011; Curioso, 2010; Elliot, 2011; Jaquet, 2010; Kamau, 2011; Li, 2010;

Lucey, 2011; Musumari, 2013; Oku, 2013; Potchoo, 2010; Saha, 2014; Senkomago, 2011). One participant in a study by Curioso (2010) stated that ""I think that forgetting to take your medicines is that you simply miss the time, because you know that you have to follow a scheme, to follow a treatment". Another statement: "Sometimes, it happens that I forget that I have already taken my evening pills; in that case I will take another one just to be sure I don't miss" (Musumari, 2013).

Travel or being away from home was found in eight articles (Curioso, 2010; Elliot, 2011; Jaquet, 2010; Oku, 2013; Potchoo, 2010; Saha, 2014; Senkomago, 2011; Vallabhaneni, 2012). Travel rose to be the second main factor of poor adherence. In a study conducted in India, majority of participants forgot to bring medicines when away from home, and changed daily routines when travelling (Saha, 2014). Pill burden was found in three articles (Nyanzi-Wakholi, 2012; O'Connor, 2013; Oku, 013) as a barrier. Studies were conducted in Nigeria (Oku, 2013), in Uganda and Zimbabwe (Nyanzi-Wakholi, 2012) and O'Connor's study which was conducted in 33 countries around the world. Barriers related to regimen characteristics were mentioned in articles from all over the world.

Treatment related adverse side-effects were found to be a barrier to adherence in 13 articles (Al-Dakkak, 2013; Badahdah, 2011; Beer, 2014; Curioso 2010; Dima,2013; Li, 2010; Lucey, 2011; O'Connor, 2013; Okonsky, 2011; Potchoo, 2010; Saha, 2014; Uuskula, 2012; Vallabhaneni, 2012 ). It was the third most commonly found barrier that rose from the literature. Side effects included both negative symptoms that the participant attributed to the ART regimen and side effects that were anticipated to occur due to the ART regimen. As highlighted by one participant in a study by Curioso (2010) "When I started with the treatment I was nauseous all the time. I had headaches. I had a fever. I had cellulitis again. I experienced a lot of illnesses that I had never had before....I was very bad off". Study by Vallabhaneni (2012) found that side effects of HAART, particularly for those on Stavudine-containing regimens were the most common reason for non-adherence. Side effects were found in studies conducted in several different countries on different continents.

Cost of acquiring antiretroviral was the fourth most common barrier found from the articles (Badahdah, 2011; Curioso, 2010; Elliot, 2011; Hanif, 2010; Musumari, 2013;

Nozaki, 2011; Oku, 2013; Potchoo, 2010; Senkomago, 2011; Tuller, 2010; Vallabhaneni, 2012 ). This includes travel cost to the facility providing the ARV and the cost of obtaining them. In a study done in the Republic of Congo (Musumari, 2010) the participants expressed difficulty securing money for transportation to attend clinical visits or other medical-related expenses such as medical tests or clinical examination fees. This resulted in some of them missing their medication refill appointments or temporarily interrupting their medication. Articles finding cost as a barrier were done in mostly in resource poor settings or rural clinics. Like in Uganda (Tuller, 2010) where a participant stated " You may fail to get the 10,000 [shillings] to bring you here, and you end up getting maybe 1000, 2000, and when you get that little, you divert it to food and some medicine, and then wait until you get enough money to bring you to the clinic".  It was found by Hanif (2010) that even within lower income population, respondents with higher levels of assets were significantly more likely to be adherent (Hanif, 2010). Vallabhaneni (2012) found, in a study conducted in India, that receiving care at a private clinic, where patients bear a greater burden of medical expenses, was associated with increased non-adherence. Lack of reminder device was found as a barrier in four articles (Elliot, 2011, Magutu, 2011; Nozaki, 2011; Van Tam, 2011), this included missing a cellphone or not owning a wrist watch. These studies were all conducted in a resource poor setting, in Cambodia (Elliot, 2011), South-Africa, in rural area (Magutu, 2011), Zambia, also in rural area (Nozaki, 2011) and Vietnam (Van Tam, 2011).

### 5.1.3  Psychosocial barriers

Stigma was the other most commonly found barrier that rose from the articles. It was mentioned in 16 (Afolabi, 2013; Badahdah, 2011; Curioso, 2010; Gustal, 2011; Kamau, 2011;  Li, 2011;  Li, 2010; Lyimo, 2014; Musumari, 2013; Nozaki, 2011; Nyanzi-Wakholi, 2012; Okoror, 2013; Peltzer, 2010; Van Tam, 2011; Wagner, 2012) out of the 46 articles. Nine of the articles mentioning stigma as a barrier were done in Africa, one in South-America and rest in Asia.  None of the articles done in the US mentioned stigma as a barrier for adherence. In a study conducted by Masumari (2013), in Congo, a participant states: "I went to live at my grandparents' place; over there they were not aware of my disease, so I didn't want them to know". In a study conducted in Peru (Curioso, 2010)

a participant states: "I have to hide from my family so they do not know that I'm taking my ART medication. They do not know anything about my disease."

Depression was found as a barrier in nine articles (Beer, 2014; Bottonari, 2010; Finocchario-Kessler, 2011; Jaquet, 2010; Kong, 2011; Nel, 2013; Saberi, 2011; Tyer-Viola, 2014; Venkatesh 2010). Six of the nine articles finding depression as a barrier were conducted in the US. Bottonaris' (2010) results illustrated that, among clinically depressed individuals, higher levels of threat associated with acute life events prospectively predicted decreases in treatment adherence. Emotional distress was mentioned in three articles (Dima, 2013; Bottonari, 2010; Finocchario-Kessler, 2011). As Bottonari (2010) found that results that suggest that many HIV-infected individuals experience substantial stress and chaos in their lives. . Drinking alcohol (five articles) and substance abuse were found as a barrier in seven articles (Beer, 2014; Jaquet, 2010; Kyser, 2011; Finocchario-Kessler, 2011; Lyimo, 2014; King, 2012; Venkatesh, 2010). Kyser et al (2011) found that persons who drank three or more alcoholic beverages per day were 70% more likely to be non-adherent compared with those who drank less.

 Seven studies (Badahdah, 2011; Dima, 2013;  Kamau, 2011; Okonsky, 2011; Uuskula, 2012; Venkatesh, 2010; Wagner, 2012) listed feeling physically very good or bad to a barrier for adherence.

| Scheduling | 16 |
|---|---|
| Stigma | 16 |
| Adverse side effects | 13 |
| Cost | 12 |
| Forgetfulness | 12 |
| Depression | 9 |
| Travel | 8 |
| Drinking of alcohol/substance abuse | 7 |
| General health status | 7 |
| Beliefs | 7 |
| Black race | 6 |
| Diagnosed long time | 4 |
| Lack of reminder device | 4 |
| Amount of pills | 3 |

| | |
|---|---|
| Availability of ARV | 3 |
| Emotional distress | 3 |
| Lack of knowledge | 3 |
| Female | 3 |
| Older age | 3 |
| Rural | 2 |
| Young age | 3 |
| Detectable viral load | 1 |
| Poor confidence | 1 |

*Table 2. Number of times a barrier was found in studies*

### 5.1.4   Patient beliefs related barriers

Belief related barriers were found in eleven, articles. These include beliefs about the antiretroviral therapy: that the medication would not help (Li, 2010; Nyanzi-Wakholi, 2012; Uuskula, 2012 ), beliefs about the need not to adhere 100% (Beer, 2014, Brown, 2013), perceiving adherence as difficult (Dima, 2013), lack of knowledge of the ART, religious beliefs (Badahdah, 2011; Jaquet, 2010), influenced by traditional healers and the use of herbal medication. The use of traditional herbal medication as a barrier was mentioned in three articles (Musumari, 2013; Oku, 2013; Peltzer, 2010) all done in African countries. Religious beliefs were both found to be a barrier and a facilitator of ART adherence. In study by Musumari  (2013) the participants belief that one's disease was caused by witchcraft led a few participants to interrupt their medication and to use prayers and/or traditional medicines in search for potential cure. In a study by Badahdah (2011) Religious beliefs were found to be a facilitator to adherence to Antiretroviral therapy In contrast to a by Finocchario-Kessler (2011) where religious/spiritual beliefs predicted lower ART adherence.

### 5.1.5   Factors having a positive influence on ART adherence

Additionally to the barriers to antiretroviral therapy several factors which have a positive influence on adherence were mentioned in several articles (See Table 3.). In 12 out (Afolabi, 2013; Curioso, 2010;  Finocchario-Kessler, 2011; Fredriksen-Goldsen, 2011; Hanif, 2013; Li, 2012; Maquu, 2011; Nozaki, 2011; Peltzer, 2010; Vallabhaneni, 2012; Van Tam, 2011; Vissman, 2013)  of the 46 articles  good social support network was

mentioned as having a positive influence on antiretroviral therapy adherence. The benefits of a strong social support network was mentioned in articles from seven different countries from four different continents. Curioso, (2010) found that family and friends remind the participants to adhere to their ART. Participant stated: "My mom or my sister remind me to take my medicines" (Curioso, 2010). Self-efficacy was mentioned in seven different articles (Beer, 2014; Brown, 2013; Colbert, 2013,; Finocchario-Kessler, 2011; Kamau, 2011; Li, 2011; Tyer-Viola, 2014) as having a positive influence on adherence to ART, four of the eight studies were conducted in the US.

| | |
|---|---|
| Social support net | 12 |
| Self-efficacy | 7 |
| Positive effects of ART | 4 |
| Knowledge | 4 |
| Fixed routine | 1 |
| Reminder tool | 1 |
| Religious beliefs | 1 |
| Reduced pill load | 1 |

*Table 3. Factors having a positive effect on ART adherence*

# 6 DISCUSSION

A meta-analysis (Ortega, 2011) of patients in North America and Africa estimated that only 55% and 77% in these areas, respectively, achieved over 80% adherence. In this review African countries had generally high adherence percentages, average of 84%, lower percentages were reported in Nigeria, Togo and South Africa. 25 out of the 28 adherence percentages were self-reported. Patient self-report data often overestimate adherence due to recall bias, it is an easy method that has been shown to be valid using electronic drug monitors and virologic failure as reference measures (Holtzman et al, 2015). The findings of this review are in accordance with previous studies where it has been found that majority of people participating in HIV programs in Africa are adherent (Kamau, 2011) and that levels of adherence are relatively high in HIV clinic studies in African countries (Halbrich, 1999). The low adherence percentage found in the US, average of 64%, is also in accordance with previous literature (Ortega, 2011). Previous research has found that adherence is a concern in North America (Mills, 2006).

Black race as a demographic barrier to antiretroviral therapy came obvious in many of the studies done in the United States. Kong (2012) states that these racial disparities may be attributed to findings that show black patients are more likely to postpone medical care, have less access to care, and less trust in health care providers than white patients. This is in accordance with previous studies (Bogart, 2010; Mkanta, 2010; Simoni, 2012). This should be further studied and adherence strategies especially in the United States should pay attention to sensitivity to cultural and socioeconomic differences. Both young age and old age were found as a barrier to adherence. The articles that found age as a barrier to adherence were conducted in The US, in different African countries and India. There doesn't seem to be a cultural aspect to age as a barrier.

In accordance with earlier studies (Giffort, 2000; Nachega 2015; Martin 2013) regimen characteristics, such as being too busy, forgetfulness, traveling and scheduling, were found to be the main barrier for adherence. These seem to be a universal issue and rose as a barrier from studies conducted all over the world, similarly in studies conducted in resource poor setting and in the western world. In a recent study conducted by Saberi et al (2015) common barriers were found to be: 'away from home' (21.9%), 'simply forgot' (19.6%), 'change in daily routine' (19.5%), and 'fell asleep/slept through dosing time' (18.9%). Forgetfulness has been identified as a major barrier to ART adherence (Wise, 2008. To increase adherence to HAART, patients can be encouraged to use the alarm systems available on their cell phones, or any other device that would be carried with them during their working hours, to provide timely reminders on taking medication (Saha, 2014). There are several studies testing reminder devices such as pagers, alarms and telephones (Hardy, 2011; Wise, 2008). This review found that not having a reminder tool was found to be a barrier in studies conducted in a resource poor setting. According to Potchoo (2011), travel as a factor of non-adherence reveals the problem of the lack of a pill container containing at least all daily doses. This review also confirms forgetfulness and scheduling issues continues to be common barriers despite the research and innovations done to eliminate these barriers. New solutions are needed to aid the patients in reaching optimal adherence. More research would be suggested in finding ways to support the patients of reminding them to take their tablets in time and support the difficulties in scheduling.

This review found that adverse side effects was the most commonly arising single barrier to adherence. Patients who had side-effects were more likely to be non-adherent, and this has also been reported in several other studies conducted in both developed and developing countries (Blake, 2000; Wasti, 2012; Weiser, 2003). It is crucial to select ART regimens that are tolerable and acceptable to patients. Drug-drug and drug-disease interactions should also be minimized as these have the potential to create additional adverse effects (Holzman, 2015). Adherence interventions need to take into account side effects, and encourage patients to talk with their care providers about side effects they may be experiencing so that treatment substitutions if available can be made.

HIV related stigma was found to be the most common barrier to ART. Internalized stigma, which is widespread among people living with HIV in sub-Saharan Africa, is also an important public health issue because it compromises ART adherence (Chen, 2015). Individuals living with HIV continue to report experiences of social isolation and discrimination resulting from being HIV positive (Kamau, 2011).Stigma has been mentioned as a barrier for adherence in several previous studies done in African countries (Weiser, 2003; Sekoni, 2012; Murrey, 2009). In accordance with these previous studies, this review found that especially studies done in the African countries found stigma to be one of the profound barriers to adherence. Efforts to counter stigma have been recognized as essential to HIV prevention and treatment (Chan, 2015). Chen (2015) found that an increases in ART coverage has led to decreases in HIV-related stigma in the general population in sub-Saharan Africa, which may, in turn, have important downstream benefits for HIV prevention and treatment.

In accordance with previous studies this review found that depression is a risk factor for nonadherence to antiretroviral therapy (Yun, 2005; Sin, 2014). Depression was found as a barrier for adherence to antiretroviral therapy in nine articles. Depression has been identified as one of the most important mental health-related barriers to ART adherence (Nel, 2011). Depression inhibits adherence due to low motivation to seek care; poor concentration resulting in forgetting to take pills on time; fatigue and loss of energy to attend clinic appointments; feelings of hopelessness about the future (Nel, 2011). Untreated depression is connected to poor adherence to antiretroviral therapy (Yun, 2005; Sin, 2014.).

This review found the cost to be a major barrier especially in resource poor countries. The cost of medical care and medications can be major barriers for patients, compromising clinic attendance and prescription fills (Holtzman, 2015). Weiser (2003) found that over-all economic situation was one of the main barriers in Botswana, most patients in Africa do not have access to subsidized or affordable ARVs. Households have been facing large financial burdens due to loss of income support from family members who die of the disease as well as increasing costs of treatment of HIV infection/AIDS and associated opportunistic infections (Weiser, 2003). In a study by Wasti (2012) money emerged as the greatest barrier, even if free-of charge ART was provided. The cost of diagnostic tests and travel costs must be paid for by patients as most respondents reported economic worries relating to the costs of transport, prescription, and charges for diagnosis.

A study by Atkinson (2009) found that with poor medication self-efficacy, incorrect beliefs about the treatment and the disease, lower optimism, and poorer understanding of treatment were associated with worse medication adherence. Wasti (2012) found that patient's beliefs regarding treatment strongly influence their medical decision-making. They found that patients who believed in the efficacy of ART are more likely to adhere. These studies support the findings of this review which found that beliefs that the medication would not help (Li, 2010; Nyanzi-Wakholi, 2012; Uuskula, 2012 ), beliefs about the need not to adhere 100% (Beer, 2014; Brown, 2013), perceiving adherence as difficult (Dima, 2013), lack of knowledge of the ART were barriers to adherence.  High self-efficacy beliefs were found in eight articles as having a positive influence on adherence to antiretro-viral therapy. Fear of doing worse without adhering to ART was a prime motivator for adherence. This review found that religious beliefs were both a barrier and facilitator of ART adherence.  Previous studies have identified beliefs in spiritual healing and/or beliefs around the causes of HIV to impact negatively on ART adherence (Musumari, 2013). Wasti (2012) found religious beliefs being a barrier, for example during Ramadan people would not take their medication.

Despite many barriers, two major factors: self-efficacy and social support, were identified as facilitators of adherence to ART. It has been found in previous studies that and self-efficacy is directly related to increased adherence (Adefolalu, 2014; Johnsson 2006;

Luszczynska, 2007; Martin, 2013). Self-efficacy can be defined as "people's self-efficacy beliefs determine their level of motivation, as reflected in how much effort they will exert in an endeavour and how long they will persevere in the face of obstacles" (Zulkosky, 2009, p101). These results highlight the importance of patients being informed, actively involved in the treatment process, and competent to manage their own treatment. In this review the most commonly found factor for supporting adherence to ART was social support. Social support from family, friends, and neighbours can help patients maintain clinic visits and medication adherence, as these supports often provide moral encouragement and healthcare assistance through transportation and reminders (Holtzman, 2015). Social support is associated with improved adherence to ART among those who disclosed their HIV status to household members or friends and acquaintance networks (Waddell, 2006).

# 7   CONCLUSION

This review found that the most common barriers to adherence to antiretroviral therapy that rose from the reviewed literature were scheduling, stigma, adverse side effects, cost and forgetfulness. The barriers have stayed much the same since antiretroviral therapy started.  The most common barriers listed by Proctor et al in 1999, were side effects and conflicts with daily routine are still the barriers which cause patients not to be able to adhere completely to antiretroviral therapy. Factors having a positive influence on adherence to antiretroviral therapy that rose from the articles review were having a good social support network and self-efficacy. It is necessary to recognize and overcome the key barriers and promote measures to facilitate adherence.

Scheduling issues, forgetfulness and adverse side effects seem to be universal barriers which rose from studies conducted all over the world.  Stigma was more prominent barrier in articles conducted in African countries and cost was found to be a barrier in studies conducted in resource poor settings.

The review found scheduling and forgetfulness being some of most common barriers in adherence to antiretroviral therapy. Solutions and innovations have been done to eradicate

these barriers. Electronic reminder devices, including cellular phones, are growing in popularity as aides for patients who take frequent medications, but there is no profound evidence found that would support their efficiency (Hardy, 2011; Wise, 2008) as these barriers still are common. The need for new solutions and innovations rose from the results of this review to support patients in scheduling issues and remembering to take pills in correct time.

In this review stigma was found to be the main barrier in adherence to antiretroviral therapy, especially in studies conducted in Africa. Efforts to counter stigma have been recognized as essential to HIV prevention and treatment (Chen, 2015). Reductions in HIV-related stigma has been successful but still people continue to present for treatment at late stages of disease, and the stigma of HIV remains a major challenge. Interventions that effectively target stigma are warranted.

Self-efficacy was found to be one of the most common positive influence on antiretroviral therapy adherence. One strategy in supporting adherence, therefore, can be to support taking antiretroviral therapy and support the belief in one's ability to cope (Martin, 2013). Consideration of how healthcare systems and policy can promote and support self-efficacy is required.

As found is this review research is usually been carried out in already adherent patients with chronically suppressed viral loads. A subject for future research would be to find those who are non-adherent and find out the reasons behind the non-adherence.

# 8  LIMITATION

It is not easy to recognize the reviews limitations as the writer of the review have been so deeply involved with the material. I have tried to retrieve the data from the articles in a consistent and systematic fashion. I have done the synthesis of the information retrieved from the articles as objectively and clearly as possible, using the data analysis chart and tables as a tool to help with the synthesis process. I have tried to present the process used as clearly as possible so that it would be easy for the reader to follow the process used.

Since the descriptive overview already includes the biases of the authors of the articles included I have tried to be unbiased in my approach to the review.

One of the strengths of the review is the large number of studies it involved and the vast material supporting the review findings. I chose to use only articles that are available online. It is difficult to know if my results would have been the same if I had chosen also articles from other sources. I chose three databases to conduct my literature search. These databases were offered free of charge by the Diaconia University of Applied Sciences library services. These databases were chosen on the basis that they offer a vast collection of full text articles.

The chosen method was descriptive literature review. There is no defined structure of writing a descriptive review. It is suggested that proper descriptive overview should critique each article included but others authors say that this is not necessary (Green, 2006). I have chosen not to do an individual critique of the articles. I chose to use data analysis chart and tables to assist in writing the results.

Weaknesses of the review are the vast differences in the studies included. The articles included studies conducted with different methods to very different sample sizes. This makes the assessment of the fact that are the findings of the individual studies comparable with each other difficult. I tried to consider this as I chose not to make a difference in the emphasis or how common each barrier was within the participants in the reviewed articles. For example forgetfulness might have been a barrier in a single study for 21.9% of the participants and another study to 12% of the participants. In the synthesis of the results I have chosen to only list the barriers mentioned in each article and not how common they were in one individual article. By reviewing the articles chosen for this literature review I have been able to find answers to my research question of currents barriers to antiretroviral therapy adherence.

All of the studies in this review were conducted, exception of one study (Masumari, 2012), to patients who were already adherent, patients attending clinics with chronically suppressed viral loads. This gives a different picture of the barriers to adherence than if the studies would have been conducted with non-adherent patients.

# 9   CRITICAL REVIEW

This thesis was done as a descriptive literature review to find out the current barriers preventing patients on antiretroviral therapy to adhere to their regimen.  It is taking research articles and forming answers to the research question by conducting a narrative overview of the reviewed articles. The thesis consists of nine parts: introduction, theoretical framework, aim of the research, research method, results, discussion, conclusion limitations and critical review.

Methodology chosen is descriptive literature review. Literature review is beneficial in providing insight into findings of other studies and forming a narrative synthesis of previously published information (Green, 2006). It is helpful in presenting a broad perspective on a topic like antiretroviral adherence. Descriptive literature reviews are great papers to read to keep up to date with currents knowledge on a subject but descriptive literature reviews are often the weakest forms of evidence for making clinical decisions in regarding patient care (Green, 2006). For this research question the method was sound as this review tries to find out the current barriers to ART adherence.

Authors of descriptive reviews are often experts of the field studied (Green, 2006), I did not have vast knowledge or experience of antiretroviral therapy before writing this review. But it is also suggested that some experts are less likely to adhere to methodological rigor when writing a descriptive literature review that non-experts (Green, 2006). I have tried my best to be objective and methodological while conducting this review.   The weakness of this methodology is that it is easy to present opinions oriented arguments rather than objective conclusions based on the arguments. The critical factor of writing a descriptive literature review is to use good methods. I found this difficult, especially in the synthesis phase where there is no systematic method to follow and provide structure. I have included a vast number of articles in the review in hopes of creating a significant knowledge base from which draw a conclusion.

Selecting the information from the primary articles is subjective, and lacks explicit criteria (Green, 2006). I chose to gather the following information from each article: the reference, country were the study was conducted, sample, method used, ART adherence

percentage, main findings on adherence barriers and comments. This information was gathered into a data analysis chart. Studies were very different in sample size and method. I was aware of this and tried to take it into consideration when choosing how to combine the information arising from different articles and synthesizing it. All of the articles included in the review and the articles supporting the findings are peer-reviewed research articles. Furthermore government agency reports and online pages are used to provide background information.

The conclusion arising from the review is supported by previous research. As stated earlier the selecting of the information from the primary articles is subjective so it is not guaranteed that another interpretation could not be plausible. But as the previous research strongly supports the review findings I am convinced I have been able to draw the correct conclusions from the data reviewed.

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# APPENDIX 1

**Appendix 1: Articles used in the literature review**

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# APPENDIX 2

**Appendix 2**. Data analysis chart

| Country | Reference | Sample | Method | ART adherence ≥95%, self-reported | Findings | Comments |
|---------|-----------|--------|--------|-----------------------------------|----------|----------|
| Nigeria, Osogbo | 1.Afolabi et l. 2013 | 379 adults-230 women, 149 men | Mix method, Descriptive cross sectional study | 87,9% | Individuals with good social support were adherent to ART. | There is need to educate and train family caregivers on stigma reduction and how to care and support their HIV positive relatives. |
| | 2. Al-Dakkak et al 2013 | | Literature review-meta analyses | | Adherence to ART was significantly lower in patients with non-specific AEs (treatment related adverse events) than in patients who did not experience AEs | Patients with specific AEs such as fatigue, taste disturbances and nausea less likely to adhere |
| Egypt | 3.Badahdah et al. 2011 | 27 women | Qualitative study, interview | | fear of stigma, costs associated with obtaining and taking ART, forgetfulness, physical discomfort from side effectshad a negative impact on their adherence. | Tremendous benefits they gained. In this study, religious beliefs acted as facilitators |

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| United States | 4.Beer et all 2014 | 3606 aduts-2636 men, 914 women, 56 transgender | Mixed method, face-to-face interviews and medical record abstractions, The Medical Monitoring Project (MMP) | 86% | Barriers for poor adherence: younger age, female gender, depression, stimulant use, binge drinking), dosing frequency, side effects. self-efficacy, beliefs about the need for adherence to prevent resistance | Poorer adherence to ART with patients diagnosed for more than 10years ago. |
| United States | 5. Brown et al 2013 | 116 adults-49 women, 67 men | Quantitative study, survey | 61% | Positive effects: adherence self-efficacy. Non adherence: women , racial minorities, beliefs that do not support a goal of 100% adherence | . |
| United States Pennsylvania, Ohio | 6. Colbert et al. 2013 | 302 adults-89 women, 213 men | Quantitative. Randomized control trial | 67,71% Electronically measure | Poor adherence to be significantly related to black race, detectable viral load and  Greater medication adherence was 2-3 number of medications, higher self-efficacy beliefs, | there is no statistically significant association between HIV medication adherence and functional health literacy |
| Peru, Lima | 7. Curioso et al 2010 | 31 adults-28 men, 3 women. Recourse poor setting | Qualitative study, In depth interview | - | Most common barriers for ART adherence: side effects, forgetting, inconvenient schedule, financial burden, travel, stigma | Facilitators for adherence: fixed routine, understanding the need for adherence, knowledge, seeing positive results, use of a reminder tool |
| Romania | 8. Dima et al 2013 | 312 young adults (18-25 years)-164 women, 148 men. | Quantitative study, Questionnaire, CEAT-VIH | 84% | Low ART adherence more likely: patients feel physically better or worse, emotionally distressed, if they perceive adherence difficult: requiring time and effort to the medication schedule, feel less satisfied | Poor adherence if have less confidence in their ability to adhere |

| | | | | | with their treatment, experience more side effects and have lower outcome expectations. | |
|---|---|---|---|---|---|---|
| Cambodia | 9. Elliot et al 2011 | 27 adults | Qualitative study, in depth interview | | attributed to forgetting, being busy, travelling or because of lack of a reminder device.<br>Availability of ART poor. | ART considered a gift, privilege. high prices in the private sector, patients sharing ART with people who had not been able to access ART or selling antiretroviral drugs in order to buy food |
| United States, Mid-west | 10. Finocchario-Kessler et al. 2011 | 204 adults-51 women, 153 men | Quantitative study, Ran-domised controlled trial | 59% | Barriers: depression, perceived stress, alcohol use, CD4 and viral load counts, frequency of dosing, social support, self-efficacy, experience with ART.<br>Facilitators for adherence: autonomous support from friends, family to make decisions regarding treatment, autonomous regulation, positive coping styles | religious/spiritual beliefs predicted lower ART adherence |
| China | 11. Fredriksen-Goldsen et al 2011 | 113 adults survey 20 adults interview | Mix –method study | | Patients with family support report superior ART adherence. Also, gender (being female) and less time since ART initiation are significantly related to superior adherence. | |
| Ethiopia, Uganda | 12. Gustal et al 2011 | 118 adults | Qualitative semi-struc-tured interview | | peer counsellors as facilitators of adherence, | avoiding or reducing stigma, also requires specific attention |

| Brazil, Rio de Janeiro | 13. Hanif et al. 2013 | 632 adults- 196 women, 429 men, 7 transgender, health clinics | Quantitative, Cross sectional survey | 84% | Having one child, high social support and high asset index has positive association with ART adherence, being a women a negative association | wealth plays a role in adherence even in the context of free health services and medication, and gender |
|---|---|---|---|---|---|---|
| West Africa, International epidemiological Database to Evaluate AIDS (IeDEA) initiative | 14.Jaquet et al. 2010 | 2920 Adults-1838 Côte D'Ivoire, 486 Benin, 596 Mali | Quantitative study, Cross –sectional study | 91,8% | Poor adherence to ART: being busy or simply forgot, being away from home, being out of stock for HAART because of the pharmacy, being out of stock of HAART at home, being depressed and being influenced by traditional healers or religious leaders | Alcohol consumption and hazardous drinking is associated with non-adherence to HAART |
| Kenya | 15. Kamau et al. 2011 | 354 adults-253 women, 101 men | Quantitative research-questionnaire | 94,5% | Reasons for lack of adherence: busy with other things, simply forgot, did not want others to notice you taking medications, felt sick, felt good, had problem taking medication at specific times ,slept through the dose. Only 1% indicated missing the dose because they ran out of pills | found a significant relationship between coping self-efficasy and adherence to ART. |
| United States | 16. Kong et al 2012 | 7034 adults- 66% black Americans, multi-state medical database | Quantitative study Retrospective cohort study | - | black race was significantly associated with decreased odds of ART adherence. | presence of depression did not further enhance the already existing racial disparity. depressed patients not on |

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| | | | | | | antidepressant had worse adherence than once one medication, also had lower adherence compared to the non-depressed patients |
| United States SUN study (n Denver, Colorado; Minneapolis, Minnesota; Providence, Rhode Island; and St. Louis, Missouri.) | 17. Kyser et al. 2011 | 528 adults-118 women, 410 men | Quantitative study,Longitudinal prospective cohort study | 84% | associated with non-adherence: black race, being unemployed and looking for work, having been diagnosed with HIV ]5 years ago, drinking three or more drinks per day, having not engaged in any aerobic exercise in the last 30 days | |
| China, Anhui provence | 18. Li et al 2012 | 66 adults-16 women, 40 men | Mixed method, interview | 81,8% | family members and friends sometimes or frequently reminded them to take medicine | not find a significant association between adherence to ART and demographic characteristics, |
| China | 19. Li et al 2011 | 202 adults-8 women. 144 male | Quantitative study | 87% | high self-efficacy for disease management was a predictor for good medication adherence, which was effected by hiv stigma | |
| Thailand | 20.Li et al. 2010 | 386 Adults- 259 women, 126 male | Quantitative study, Cross sectional survey | 69% | Poor adherence due to: forgetting, afraid of stigma if their HIV status was disclosed, : trouble visiting the doctor, running out of medication, not understanding the medication or believing that the medication would not help, being | the presence of depressive symptoms proved to be a barrier to ART adherence. Better access to care, positive family communication and HIV disclosure were significantly associated |

| | | | | | too sick to retrieve the medication from the hospital, wanting to avoid side-effects. | with better ART adherence |
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| United States | 21. Lucey et al 2011 | 46 adults-7women, 39 men, with sensory neuropathy and HIV | Quantitative study, questionnaire | | Fear f side effects and forgetfulness, which was related to pain poor adherence | |
| Tanzania | 22. Lyimo et al 2014 | 158 adults | Quantitative study, interview, structured questionnaire | 100% | adherence was negatively affected by alcohol use, self-stigma, and denial | |
| South Africa | 23. Maqutu et al 2011 | 688 adults- | Quantitative study, data analysis | 79% pill counts data | negative association HAART adherence time interval between successive clinic visits. cell phone ownership, living with a partner, two-way interaction terms, reason for taking an HIV test, age with gender and educational level were still associated with optimal adherence | rural site, patients able to maintain high levels of adherence with longer intervals between successive visits |
| United States, Houston | 24. Marks King et al 2012 | 326 adults-91 women, 235 men Low-income | Quantitative study, Randomised controlled trail | 60,4% | the level of nicotine dependence, illicit drug use, alcohol use, and older age were each significantly associated with nonadherence to ART. | |
| Democratic Republic of Congo | 25. Musumari et al 2013 | 38 adults-24 women, 14 men | Qualitative study-semi-structured interview | | Food insecurity, financial constraints, forgetfulness, fear of disclosure main reasons for poor ART adherence | Patients with re-treatment and lost –to follow up were also interviewed |
| South Africa | 26. Nel et al 2013 | 101 adults-83 women, 18 men | Quantitative study | | non-perfect adherence were approximately three | |

| | | | | | times more likely symptoms of depression | |
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| Zambia-rural area | 27. Nozaki t al 2011 | 518 adults-297 women, 206 men | Quantitative study- semi structured interview | 88% | Non adherence: younger age, higher travel expenses, stigma, time of dose from the position of the sun, pressure to share ARV. | Positive to adherence: family support |
| Uganda & Zimbabwe | 28. Nyanzi-Wakholi et al 2012 | 82 Adults- 42 women, 40 men | Qualitative study, focus group discussion | | fear of deteriorating. Stigma, amount of pills | |
| Strategies for Management of Antiretroviral Therapy (SMART) study. Data from the SMART study were collected in 33 countries on 6 continents | 29. O'Connor et al. 2013 | 5472 | Randomized trial, quantitative | Over 80% | suboptimal adherence were black race, protease inhibitor–containing regimens, greater pill burden, higher maximum number of doses per day, and smoking. associated with higher adherence: older age, higher education, region of residence, episodic treatment, higher latest (at the time of adherence) CD4+ T-cell count, and being prescribed concomitant drugs | found that among PI/NNRTI drugs, ATV, ATV/r, FPV, IDV, IDV/r, and LPV/r were associated with suboptimal adherence, compared with EFV. LPV/r and IDV are typically believed to be associated with higher rates of side effects and were prescribed with twice daily dosing during the study period |
| United States | 30. Okonsky 2011 | 558 adults-119 women, 439 men | Quantitative study | | a PI (protease inhibitor)based regimen, symptom experience, other health conditions are reasons for missed medication, wanting to avoid side effects, felt sick or ill, too many pills to take, felt depressed/overwhelmed, and | |

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| Nigeria, Southwest | 31. Okoror et al. 2013 | 35 adults -18 women, 17 men | In depth interviews, qualitative research | | Fear for Pre ART sickly looking physical manifestation created stigma was a paramount factor for adhering to ART. | belief about adhering to ART as the way to avoid anticipated stigma |
| Nigeria, Cross river | 32. Oku et al, 2013 | 411-282 women, 129 men | Qualitative study, Cross sectional study | 59,9% | Main reasons for non-adherence to ART: being busy ,simply forgetting ,depression, frequent travelling and inconvenient timing for medications schedule | Positive effects on adherence: non use of herbal remedies, obtaining free ART services, perceived improvement in health status, and reduced pill load. |
| South Africa, Kwa-zulu-natal | 33. Peltzer et al 2010 | 735 adults-219 women, 516 men | Qualitative, Cross sectional study, interview with a questionnaire | 82,9% | Urban residence three times higher adherence compared to rural residence. Factors for high adherence: Adequate physical structure, physical health, information. Lower adherence: discrimination, poor social support, use of herb medications for HIV. | Factors explaining difference between rural and urban: transportation, access to health services |
| West Africa, Togo | 34. Potchoo et al. 2010 | 99 adults- 76 women, 23 men. | Qualitative, Crossed sectional survey, structured interview | 62,92% | Main causes of non-adherence: Forgetting, travel, cost, side-effects. | Strengthening of counselling, education and information interventions to overcome potential barriers for adherence |
| United States | 35. Saberi et al 2011 | 2845 adults-736 women, 2109 men | Quantitative data analysis | | African Americans higher odds of nonadherence in comparison to Whites. , depression associated with | |

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| India, West Bengal | 36. Saha et al 2014 | 370 adultas-154 women, 213 men. Recourse poor setting | Qualitative, Cross sectional study | - | Main causes for non-adherence: forgetting to take the medicine, being away from home, busy with other thing | positive family history of HIV was found to be the strongest predictor of non-adherence to ART also the presence of side effects with highlight that the quality of counselling in the ART centre needs to be improved. |
| Uganda, Kayunga | 37. Senkomago et al. 2011 | 140 Adults-93 women, 47 men | Qualitative study, interview | 86,4% | Barriers to adherence: being away from medication at dose time, forgetting to take pills. Lack of access to food and transportation costs | Patients attending rural clinic were significantly less adherent |
| Unganda, South West Africa, Mbarara | 38. Tuller et al 2010 | 41 adults-25women, 16 male using a regional distribution point for ARV | Qualitative study, Semi-structured interview | - | The lack of funds for monthly clinic visits to pick up ARV major barrier for adherence | Despite high motivation for treatment, lack of money priority |
| United States | 39. Tyer-Viola et al 2014 | 382 women | Quantitative study, survey | | Adherence self-efficacy had appositive influence on adherence and depression symptoms negative | |
| Estonia | 40. Uuskula et al. 2012 | 144 Adults- 58 women, 68 men | Mixed method Cros-sectional study, interview survey+data abstraction | 88% | barriers to ART include beliefs about the need for treatment and concerns about adverse effects, general health status (health less than good or good), | active or historical IDU was not predictive of non-adherence. alcohol use was not identified as an influential factor on ART adherence |

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| India, Banhgalore | 41. Vallabhaneni et al. 2012 | 552 adults-177 women, 375 men | Quantitative study, interview | 80% | Negative effects on adherence: efavirenz-based therapies (used usually with tubercoloses infected patietns), being unmarried, Side effects, Cost (private-clinic patients) | ''being busy with other things'', and ''being away from home'',longer duration of treatment, |
| Vietnam | 42. Van Tam et al. 2011 | 48 Adults-12 women, 6 men | Qualitative study, interview | | Stigma was identified as a strong barrier to ART adherence, logistical barriers. reminders decreased over time and this could lead to a reduction in ART adherence strong desires for adherence support,  PLHIV peer-support | participants did not want to receive ART medications at home, as they feared it might increase the risk of HIV-related stigma |
| South India | 43. Venkatesh et al. 2010 | 198 Adults-62 women 136 men | Quantitative data review | 50,5% | Factors for nonadherence: poor general health, distress, alcohol use. | higher CD4 cell counts and a longer time period of HAART experience were less likely to be adherent, |
| Unites States North Carolina | 44. Vissman et al 2013 | 66 adults- 19 women, 47 men. Latino immigrants | Qualitative, Structured interview | 71% | Social support was significantly and inversely associated with adherence, | |
| United States Los Angeles | 45. Wagner et al. 2012 | 214- adult men African American | Quantitative study Interview | 22% electronic monitoring | Older and more formal education associated with better adherence. Post traumatic stress was not indicator of poor adherence. however, as symptoms become more severe, adherence significantly declines | A greater number of discrimination experiences from being gay, African American, or HIV-positive were negatively correlated with adherence. |

| Tanzania Free clinic | 46. Watt et al. 2010 | 340 adults-252 women, 88 men | Qualitative study, in-depth interviews | 94% | Poor adherence: old age(over 50), young age (under 30), h less favoura-ble assessments of their in-teractions with providers, ever missing a clinic ap-pointment | |
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