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Faculty of Community and Health Sciences

MINI THESIS

Title: Transition interventions for adolescents on antiretroviral therapy on transfer from
pediatric to adult healthcare: A systematic review

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The logo of the University of the Western Cape, featuring a classical building facade with columns and a pediment, with the text 'UNIVERSITY of the WESTERN CAPE' below it.

Key words: Systematic review, Transition, Interventions, HIV, Antiretroviral therapy,
Retention in Care, Viral suppression, Pediatric, Adolescent, Outcomes

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the University of the Western Cape.

ABSTRACT

Adolescents living with HIV (ALHIV) experience poor health outcomes such as low retention in care, suboptimal adherence to ART, insufficient viral suppression, high morbidity and mortality. These outcomes coincide with the period during and after their transition from pediatric to adult healthcare. Several studies have been conducted to describe and assess the effects of transition interventions for ALHIV predominantly in high-income countries. The dearth of studies on transition interventions in sub-Saharan Africa can be attributed partly to a lack of national guidelines and clinical protocols to guide the transfer of ALHIV on ART from pediatric to adult healthcare.

This study aimed to systematically describe the compendium of transition interventions and synthesize the effects of such transition interventions on adherence to ART, retention in care and viral load suppression.

Seven databases and Google Scholar were searched using a well-formulated search strategy, which comprised keywords such as HIV, antiretroviral therapy, adolescents, pediatric, adult and healthcare transition. The findings of this review were reported according to the Preferred Reporting Items Stipulated for Systematic Reviews and Meta-Analyses 2020 statement. The risk of bias and strength of evidence was assessed using the National Institutes of Health quality assessment tool for observational cohort and cross-sectional studies.

Seven studies (two cross-sectional, two retrospective cohort and three prospective cohort studies) - with sample sizes ranging from 13 to 192 were included in the narrative synthesis because there was high heterogeneity amongst studies. Hence, meta-analysis was not possible. Six interventions were implemented to support the transition to adult care program, namely: individualized care plan, group transition, communication between pediatric and adult clinic, psychological support, health and sexual education, and mHealth. Three studies were rated as good quality (low risk of bias); one as fair quality (moderate risk of bias); and three as poor quality (high risk of bias).

There is high quality evidence that *individualized care plans* improved adherence, retention in care and viral load suppression in six of the studies at post-transition over short and long term. There was weak evidence for the effectiveness of the *group transition* intervention on viral load suppression and retention in care at six years post-transition. There was high quality of evidence that interventions that involved *communication* between sending and receiving health staff and between adolescents and receiving health staff, *psychological support*, and *health and sexual education* improved adherence, retention in care and viral load suppression post-

transition over short and long term. There was high quality of evidence that a *mHealth* intervention improved retention in care and viral load suppression post-transition over short and long term.

We strongly recommend transition interventions that include a combination of individualized care, communication between sending and receiving staff, psychological support, health and sexual education and a mHealth approach to improve treatment outcomes for adolescents on ART. We recommend further rigorous research to determine the effectiveness of group transition interventions on treatment outcomes for adolescents on ART.

KEYWORDS

Transition Interventions

Antiretroviral therapy

Adherence

Retention in Care

Viral suppression

Adolescent

DECLARATION

I declare that *Transition interventions for adolescents on antiretroviral therapy on transfer from pediatric to adult healthcare: A systematic review* is my own work, that it has not been submitted for any degree or examination at any other university and that all sources I have used or quoted have been indicated and acknowledged as complete references.

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Signed:



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DEDICATION

This work is dedicated to God Almighty, who has helped me throughout my studies and continuously inspires me whenever I get stuck.

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Definitions

Transition: "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child/adolescent-centered to adult-oriented healthcare systems" (Blum et al., 1993:1).

Interventions: an intentional action (singular or constellation) designed for an individual, a community, or a region that alters behavior, reduces risk, or improves the outcome (Schillinger, 2010).

Adherence: "patient's ability to follow a treatment plan, take medications at prescribed times and frequencies and follow restrictions regarding food and other medications" (Horizons/Population Council, 2004).

Retention in care: "continuous engagement from diagnosis in a package of prevention, treatment, support and care services" (World Health Organization (WHO), 2012:3).

Viral suppression: defined as "suppressing or reducing the function and replication of a virus" (Boskey, 2020). Different thresholds such as ≤ 20 , ≤ 50 , ≤ 200 and ≤ 400 copies of HIV per milliliter of blood have been used in the literature to measure viral suppression (Lesko, Chander, Moore, & Lau, 2020). However, < 200 copies of HIV per milliliter of blood has been suggested by Centers for Disease Control and Prevention as the threshold at which viral suppression is established (CDC, 2019; Zanoni et al., 2021).

Pediatric: a branch of medicine that deals with children and their diseases (Oxford Advanced Learners Dictionary, 2021).

Adolescent: a young person in "a distinct period of human development—a transitional period between the two developmental epochs of childhood and adulthood (Hopkins, 2014). The United Nations defines the adolescent age as between 10 and 19 years (WHO, 2014).

Abbreviations

ART	Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
ALHIV	Adolescents Living with Human Immunodeficiency Virus
UNICEF	United Nations International Children's Emergency Fund
UNAIDS	United Nations Programme on HIV/AIDS
CDC	Centers for Diseases Control and Prevention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CD4+	Cluster of Differentiation 4

CHAPTER 1: INTRODUCTION

1.1 Background

Poor health outcomes among adolescents living with HIV (ALHIV) are a global public health concern. Despite a global decrease of 74% in annual AIDS-related deaths among children (0-9 years) since its peak in 2003, only a 6% decrease has been observed in adolescents (10-19 years) (UNICEF, 2020). In 2019, an estimated 34,000 adolescents living with HIV died and some 170,000 were newly infected (UNICEF, 2020). Most of these deaths and new infections occurred in Sub-Saharan Africa, where the epidemic is primarily concentrated (UNAIDS, 2020). Poor outcomes such as low retention in care, low rates of viral suppression, high morbidity and mortality among ALHIV have been associated with suboptimal adherence to antiretroviral therapy during the adolescents' transitioning period (Badejo et al., 2018; Jerene, Abebe, Taye, Ruff & Hallstrom, 2019; Pinzón-Iregui, Ibanez, Beck-Sagué, Halpern & Mendoza, 2017).

Transition is defined as “*the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child/adolescent-centered to adult-oriented healthcare systems*” (Blum et al., 1993:1). The transition of care happens at a critical time in adolescents' lives when significant physiological and psychological developments occur in the individual (Adejumo, Malee, Ryscavage, Hunter & Taiwo, 2015; Campbell et al., 2016). It is widely accepted that adolescence is when adulthood habits are established (Sawyer, Azzopardi, Wickremarathne & Patton, 2018). During this time, the adolescent's HIV statuses are disclosed to them as they are prepared to leave the comfort of the pediatric clinic to unfamiliar territories of adult healthcare that may expose them to discrimination and stigmatization (Njuguna et al., 2019; Tanner et al., 2016). Adolescents must grapple with different truths and exposures as they are required to become increasingly self-dependent in managing their HIV condition. A structured transition is widely considered to be vital for the continuity of care and persistent engagement in care among ALHIV.

Studies have described transition interventions from pediatric to adult healthcare in adolescents with chronic conditions such as diabetes mellitus, spina bifida, epilepsy and cystic fibrosis, but few studies described the transition to adult care for ALHIV (Betz, 2004; Brumfield & Lansbury, 2004; Freed & Hudson, 2006; Lewis-Gary, 2001; Maturo et al., 2011; Por et al., 2004). The studies on structured

transition interventions for ALHIV have been conducted predominantly in high-income countries (Njuguna et al., 2020). While some transition interventions led to a substantial reduction in poor health outcomes among ALHIV, others have reported no significant reduction (Judd, Sohn & Collins, 2016). This inconsistency could result from the interventions' limited scope and generalizability (Gabriel, McManus, Rogers & White, 2017). Also, the effectiveness of transition interventions in adolescents living with HIV are assessed by measuring an increase in CD4+ T-lymphocyte count, viral load suppression, reduction in mortality, higher adherence to therapy and better retention in care (Lolekha et al., 2017; Wiener, Zobel, Battles & Ryder, 2007). Only a few studies in sub-Saharan Africa assessed the effectiveness of these interventions because validated tools are lacking (Njuguna et al., 2019). In addition, national guidelines and clinical protocols for ALHIV are lacking in most sub-Saharan Africa countries where most ALHIVs are domiciled (Dahourou et al., 2017). Yet, structured transition interventions can channel the path for ALHIV to successfully transition into adulthood (Njuguna et al., 2019).

1.2 Problem Statement

Systematic reviews on impact, effectiveness and treatment outcomes on transition interventions in adolescents with chronic diseases have been reported in the literature, but none of these studies focused on ALHIV (Campbell et al., 2016; Chu, Maslow, von Isenburg & Chung, 2015; Gabriel et al., 2017). To date, no systematic review has been conducted to describe transition interventions for ALHIV or document the evidence of the effects and effectiveness of such interventions. This is a critical gap in the literature because later adolescents report the worst treatment outcomes on ART (Judd et al., 2016; Njuguna et al., 2020). Systematically reviewing these interventions can provide robust information on the strength of evidence from which recommendations for policy and practice can be made (Antman, Lau, Kupelnick, Mosteller & Chalmers, 1992; Oxman & Guyatt, 1993). Also, describing and synthesizing evidence on the effects of transition interventions targeted at ALHIV will explain what works and inform reliable best practices, such as developing sound protocols that can be implemented and bringing about better health outcomes for ALHIV.

1.3 Aims and Objectives

This study aims to systematically describe interventions to guide the transition of adolescents on antiretroviral therapy (ART) on transfer from pediatric to adult care, assess the strength of evidence

on the effects of the interventions on adherence to antiretroviral therapy, retention in care and viral load suppression and make recommendations.

The objectives of the study are to:

- Describe the transition interventions designed to improve health outcomes of adolescents on ART on transfer from pediatric to adult healthcare.
- Appraising the quality of studies that measure the effect of transition interventions in adolescents on ART on adherence to ART, retention in care and viral load suppression.
- Make recommendations for transition interventions by assessing the strength of evidence.

1.4 Review question

What are the effects of transition interventions to improve health outcomes among adolescents on ART transitioning from pediatric to adult healthcare?

1.5 Thesis Overview

This first chapter presented the introduction to the topic and highlighted the rationale, aim, objectives and research question for the review. The justification for conducting this review was also highlighted.

Chapter 2 discusses in detail what is currently known in the literature regarding transition interventions focused on adolescents on ART on transfer from pediatric to adult. It expounded on the different treatment outcomes of interest in this study. The types of transition interventions currently available were discussed and factors that influence health outcomes in adolescents on ART were duly discussed.

Chapter 3 details the methodology used in the current study. This included the eligibility criteria (inclusion and exclusion) and the search strategy to identify relevant publications. A detailed process of the study selection process was explained. The chapter presented the data extraction process and how included studies were critically appraised. The ethical considerations for the study were equally documented.

Chapter 4 presents the details of the study's findings. It described the literature search, characteristics of the studies that were included, the risk of bias judgment and quality assessment of the included

studies. It also gave a detailed summary of all the transition interventions and their respective outcomes.

Chapter 5 presents the final chapter of this review. The findings from the previous result chapter were discussed. The implication of the findings and recommendations were provided for clinical practice, Public Health practice and research. Lastly, the study's limitations were highlighted and a conclusion section was provided.

CHAPTER 2. LITERATURE REVIEW

2.1 Introduction

The first section discusses the outcomes of interest for adolescents on ART, namely adherence, retention in care and viral load suppression. The second section synthesizes types of transition interventions. This is followed by highlighting the transition outcomes. It then explained the different measures of transition success. In conclusion, it discusses the different transition interventions available in the literature and expounds on each element.

2.2 Outcomes of interest for adolescents on antiretroviral therapy

Extant pieces of literature have identified the three primary outcomes of interest among ALHIV to be adherence to ART, retention in care and viral load suppression (Iacob, Iacob & Jugulete, 2017; Mukumbang, van Wyk, Van Belle & Marchal, 2019; Nachega et al., 2014; Phelps, Hathcock, Werdenberg & Schutze, 2010; WHO, 2012).

2.2.1 Adherence

Adherence can be defined as the process by which HIV patients take their medication (antiretroviral drugs) as prescribed (Vrijens et al., 2012). Adherence to ART of at least 95% (for a daily single-pill regimen - 14 non-sequential missed doses over a year) is recommended as optimal adherence. At the same time, anything below is considered a suboptimal/poor adherence to ART (Neupane, Dhungana & Ghimire, 2019). Varied adherence to ART measurements exists in the literature and these include viral load, self-report, pill count, home record, pharmacy refill, healthcare provider assessment or electronic monitoring (Hudelson & Cluver, 2015). Adherence to ART predetermines successful viral suppression in HIV patients (Iacob et al., 2017). This is because an adequate concentration of HIV drugs in the blood may reduce plasma viral load by suppressing the virus replication (Phelps et al., 2010). Suboptimal adherence to ART can lead to viral progression, viral resistance and opportunistic infections. As prescribed, continuous adherence to ART leads to viral load suppression, which increases the immune system functioning and decreases the risk of onward HIV transmission (Agwu & Fairlie, 2013).

2.2.2 Viral load suppression

HIV viral load is the amount of human immunodeficiency virus in the blood of an HIV-infected individual. The point at which ART has reduced or suppressed the replication ability and the quantity of the virus in the blood to a low level is described as viral load suppression (Boskey, 2020; Phelps et al., 2010). Yet, there is variation in viral suppression definition (Lesko, Chander, Moore & Lau, 2020). Different thresholds such as ≤ 20 , ≤ 50 , ≤ 200 and ≤ 400 copies of HIV per milliliter of blood have been used in the literature to determine viral load suppression (Lesko et al., 2020). However, < 200 copies of HIV per milliliter of blood has been suggested by the Centers for Disease Control and Prevention (CDC) as the threshold at which viral suppression is achieved (CDC, 2019; Zanoni et al., 2021). Adolescents and adults with viral load suppression are less likely to transmit HIV or develop HIV-related health challenges (Iacob et al., 2017). Viral load measurement can be used to monitor treatment effectiveness because continuous adherence to ART is confirmed to bring about viral load suppression (Iacob et al., 2017; WHO, 2012).

2.2.3 Retention in care

Retention in care can be defined as the continuous engagement in medical care in a health facility after the initial contact with the system (National HIV Curriculum, 2021). Also, the WHO 2012 defines retention in care as the “*continuous engagement from diagnosis in a package of prevention, treatment, support and care services*” (WHO, 2012:3). Different standard bodies have posited different measurements of retention in care. For example, it was defined by the CDC as having at least two CD4 cell counts or viral load tests performed in the space of 3 months during the assessment year (CDC, 2020). On the other hand, the Institute of Medicine defines its measurement in terms of medical visits, which is nothing less than two medical visits every 12 months, with at least 90 days between visits (Rebeiro et al., 2014).

In summary, retention in care can be measured by considering laboratory criteria, clinic visits, missed visits, appointment adherence, visit constancy and gaps in care (Mugavero, Davila, Nevin & Giordano, 2010; National HIV Curriculum, 2021). Good retention in care has been found to correlate strongly reduced viral load in the blood and hence, better treatment outcomes in adolescents and adults (Sabin et al., 2017). In contrast, poor retention in care has been associated with non-viral suppression and a high mortality rate (Giordano et al., 2007; Mugavero et al., 2009; Mugavero et al., 2014).

2.3 Definition of transition

Transition can be defined as "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child/adolescent-centered to adult-oriented healthcare systems" (Blum et al., 1993:1). Transition is a series of processes that spans disclosure of HIV status through preparation to transfer and eventually the actual transfer to the adult clinic (Committee on Pediatric AIDS, 2013). The transition of care happens at a critical time in adolescents' lives when significant physiological and psychological developments occur in the individual. Therefore, it requires multipronged interventions to ensure its success.

2.4 Types of transition interventions

Transition interventions are structured and designed to improve the health outcomes of adolescents and young adults with chronic health challenges pre-, during and post-transfer from child/adolescent healthcare to adult healthcare (Committee on Pediatric AIDS, 2013; Jones et al., 2019).

Pre-transfer interventions prepare adolescents for transfer from pediatric to adult clinics. It mostly happens within the child/adolescent facilities and is run by multidisciplinary healthcare professionals. These interventions could start with early disclosure of HIV status to clients (even before adolescence) (The Committee on Pediatrics AIDS, 2013; Hansudewechakul et al., 2015; Mbalinda et al., 2021). The adolescents are offered support to accept their disclosed status and the necessary responsibilities that come with it. The support could be in the form of individualized counseling (Mbalinda et al., 2021; Righetti et al., 2015). Adolescents are also introduced to the idea of transition and gradually prepare for the transition by assessing their HIV and health-related knowledge to ensure their transition readiness (Lolekha et al., 2017; Sturgeon et al., 2020). A transition readiness scale can be used to gauge transition readiness, such as level of anxiety, fear of transition, fear of stigma and discrimination in adult clinics, privacy and confidentiality (Fair, Sullivan, Dizney & Stackpole, 2012; Mbalinda et al., 2021; Wiener, Zobel, Battles & Ryder, 2007). These interventions flow into the during-transition interventions.

The *during-transfer* interventions focus on improving HIV and health-related knowledge and ART, enhancing self-efficacy, coping tactics and psychological skills, helping with sexuality

problems, promoting independence and easing fears associated with a transition. To improve HIV health-related and ART knowledge, educational sessions could be held as a group or one-on-one. In these sessions, adolescents are taught topics such as HIV infection, its clinical manifestations, risks, transmission routes and prevention measures and principles of ART and adherence (Continisio et al., 2020). Self-efficacy could be enhanced by providing educational life skills and support groups. The educational life skills could involve how to adhere to treatment, ways to seek employment for older adolescents and how to access health insurance and financial aid, while support groups could be in the form of peer/family/community providing emotional and social support to ALHIV (Biersteker et al., 2016). A psychologist experienced in pediatric HIV management could be part of the multidisciplinary team to provide coping tactics and psychological skills. The psychologist meets with adolescents and their families regularly to discuss and provide care as needed (Continisio et al., 2020). To help with adolescents' sexuality challenges, an intervention included the services of a sexologist who is independent of clinic staff (Westling et al., 2014). Hence, allowing adolescents to discuss their sexuality challenges freely and learn coping tactics to deal with them simultaneously. To promote independence and allay fears associated with transition, transition interventions could include communication between pediatric/adolescent and adult providers. This communication includes adolescents being introduced to and having a full consultation with adult healthcare personnel within the pediatric/adolescent clinic and assistance provided for adolescents to overcome system-level barriers such as insurance changes or social services (Fair, Sullivan & Gatto, 2010; Gilliam et al., 2011). Familiarization of adolescents with different sections of the adult clinic is also of utmost importance (Mbalinda et al., 2021). The intervention could also involve personalizing healthcare appointments and ART per adolescent's needs (Continisio et al., 2020; Righetti et al., 2015). Also, adolescents are given education on self-managing their medications and the importance of being adherent to treatment (Righetti et al., 2015). On their first visit to the adult clinic, a social worker/pediatric staff could also be present to guide and help clarify unclear issues (Tanner et al., 2018).

Post-transfer interventions are implemented after transitioning from pediatrics/adolescents to adult clinics. They occur in adult clinics and are more focused on assessing transition outcomes. Immunological (CD4+ counts) and virological (Viral load) measurements are taken and then compared with their before-transition values to assess treatment outcomes. Also, transition experiences of ALHIV are gauged. These measurements are done to inform better strategies to transition ALHIV and examine if the transition was successful or not (Hussen, Chahroudi,

Boylan & Andres, 2014). A study has noted that post-transition intervention should not stop at assessing transition outcomes. Post-transition interventions could go further in making sure there is an availability of a social worker at the adult clinic who provides support to adolescents for the first year of their transfer to the adult clinic (Biersteker et al., 2016).

2.5 Measures of transition success

Different measures are recommended as best practices for evaluating treatment outcomes following transition for adolescents and adults on ART. These can be applied in assessing the success of transition or transition interventions. These markers are (1) immunological (CD4+ T-cell counts), (2) virological (viral load) and (3) behavioral (treatment adherence and retention in care). They help ascertain the success of transition interventions (Fair, Sullivan & Gatto, 2011; Jones et al., 2019). Studies measure these markers during and post-transition to ascertain treatment and transition intervention efficacy. In addition, psychosocial support, clinic utilization, self-efficacy and psychological support are used to gauge the success of transition or transition interventions (Righetti et al., 2015; Continiso et al., 2020; Griffith et al., 2019).

2.5.1 Immunological and virological markers

Several studies have reported that poor virological, clinical and immunological status (viral non-suppression, low CD4+ nadir and CD4+ count) at transition have been associated with increased poor health outcomes after transition (Cordova, Caillaud & Rodriguez, 2020; Aquilera-Alonso et al., 2020; Collins et al., 2017; Judd et al., 2017). In contrast, high CD4 count, low viral load, WHO stage I/II, CDC stage I/II at transition predicts a better treatment outcome post-transition (Badejo et al., 2018; Okoboi et al., 2016; Weijnsfeld et al., 2016; Sohn et al., 2020). Asad et al. (2020) concluded that young people who transitioned to adult care with poor immunological markers and advanced disease progression were at greater risk of AIDS and mortality in adult care.

Studies have also shown improved virological and immunological status at transition over the years. This improvement is due to better and new ART treatments for adolescents (Aquilera-Alonso et al., 2020; Collins et al., 2017). This was highlighted by a UK study that reported that adolescents with later birth years have a higher CD4 count at transition, suggesting improvements in clinical care and/or transition planning over time (Judd et al., 2017).

2.5.2 Behavioral measures

Adolescents and adult demeanor influence behavioral measures to their treatment. These measures include treatment adherence and retention-in-care (Jones et al., 2019). Extant literature has reported that poor adherence to ART leads to poor immunological and virological outcomes for adolescents on ART (Freitas et al., 2019; Judd et al., 2017). These outcomes lead to HIV advance progression and may eventually lead to death (Asad et al., 2020). However, a study conducted in Nairobi reported that good self-esteem is positively associated with ART self-efficacy, leading to optimum adherence amongst ALHIV (Gitahi et al., 2021). However, the adherence measurement in the study was self-reported. They indicated that higher ART self-efficacy could be a predictive tool for optimal clinical outcomes during the adolescent transition to adult HIV care (Gitahi et al., 2021).

Several studies have reported poor retention in care among adolescents on ART post-transition (Ryscavage et al., 2016; Tsondai et al., 2020). A United States study reported only 50% retention in care even with an excellent linkage to care among the young adults (Ryscavage et al., 2016). Also, a South Africa study reported a decline in retention in care among all transition-age thresholds post-transition (Tsondai et al., 2020). Nevertheless, increased self-management before transition has been shown to correlate strongly with retention in care post-transition (Tassiopoulos et al., 2020).

Some other transition studies have measured adolescents' and young adults' transition readiness by routinely assessing transition readiness in line with the recommendation by the American Academy of Pediatrics for effective transition (Jones et al., 2019).

2.5.3 Assessment of transition readiness

Adolescents and young adults who are excited/feel ready about transition have better treatment outcomes post-transition (Kennedy et al., 2020; Mbalinda et al., 2021). Transition studies have reported that unpreparedness or inadequate preparedness for transition could result in cART non-adherence and loss to follow-up among adolescents. A study conducted in Canada reported that only 60% of participants (young women) felt prepared for transition (Kennedy et al., 2020) despite suggesting a robust transition preparation for close to a decade. This study also found that a higher CD4 count was associated with transition preparedness. Likewise, an Ugandan study reported that transition readiness is very low (6.5%) (Mbalinda et al., 2021). Another

study in Asia reported 48% of ALHIV noted readiness/vital preparedness for transition even though 90% were involved in the preparatory discussion on transition (Sohn et al., 2019). A study in the United States incorporated the Transition Readiness Assessment Questionnaire (TRAQ) in clinical services for 22–24 years. This study found that although the overall clinical intervention for this age group transitioning to adult care might not have increased, providers could identify lacking skills and knowledge not previously addressed. These findings will help plan clinical interventions tailored towards individual needs in the future (Jones et al., 2019). They noted that TRAQ's use was positively associated with the provider's interventions towards medication management.

Contrary to this finding, a study conducted in Tanzania stated that TRAQ and other transition readiness tools used in the high-income countries might not be applicable in the sub-Saharan Africa context. They further explained that it could be because they are resource-demanding and cannot account for the differences in culture, institutions and systems (Masese et al., 2019). Recently, a South African study has proffered a solution to these differences by designing and validating a transition readiness tool for adolescents named - HIV Adolescent Readiness to Transition Scale (HARTS) questionnaire (Zanoni et al., 2021). The scale is based on four domains of transition readiness. These are disclosure, health navigation, self-advocacy and health literacy. This scale helps to determine adolescents ready to transition to adult care and those who might need additional intervention before they can transition. It also predicts viral load suppression after a year post-transition (Zanoni et al., 2021). The HARTS questionnaire has provided a platform to gauge transition readiness in similar sub-Saharan African settings and adapted to others.

2.6 Transition support interventions

Several transition support interventions have been documented in the literature. The most common approaches include support for disclosure of HIV status, support from multidisciplinary/interprofessional team, individualized care plan, education, communication, peer groups, family support, psychological support and support for transition readiness.

2.6.1 Support for Disclosure of HIV status

HIV disclosure to HIV-infected adolescents is one of the most difficult hinderance in their treatment management (Kranzer et al., 2017). Yet, adolescents who knew their HIV status are more likely to transition to adult care than those who do not know (Broström, Andersson, Hallström & Jerene, 2020). To mitigate this bottle neck in the treatment of HIV-infected adolescents, early disclosure of HIV status has been well identified in the body of literature as a good practice pre-transition (The Committee on Pediatrics AIDS, 2013; Hansudewechakul et al., 2015; Mbalinda et al., 2021). A study that reported a 73% retention in care and 78% viral load suppression mentioned that a process of HIV disclosure happens in pediatric clinic between ages 7 and 10; some years before adolescence (Hansudewachakul et al., 2015). The support interventions for HIV disclosure are targeted at supporting adolescents to accept and understand their health status and the responsibilities that come with it. A psychologist knowledgeable in pediatric HIV management guides the disclosure process and helps provide adolescents with HIV and HIV-related knowledge.in monthly meetings and group sessions with the adolescents and their families (Continisio et al., 2020). Adolescents on ART are also encouraged to disclose their HIV status to others as those who do are more likely to be transition ready than those who do not (Mbalinda et al., 2021).

2.6.2 Support from Multidisciplinary/Interprofessional team

Generally, a multidisciplinary/interprofessional team is formed (Tanner et al., 2016). This team could include nurses, doctors, social workers, psychologists, and sexologists. The team helps develop and implement a formal transition protocol (Ryscavage et al., 2016; Tanner et al., 2016; 2018). This transition protocol development is deemed better when it includes the input of adolescents on ART and their families (Badejo et al., 2018). These professionals also serve in their different capacities to care for the adolescents and provide a regular review of individual ALHIV (Jones et al., 2019). They also help prepare patients for the transition by delivering skills development and medication management services (Mbalinda et al., 2021; Tanner et al., 2016).

2.6.3 Individualized Care Plan

The care rendered to adolescents on ART in the transition process is mostly personalized as different adolescents on ART have different realities (Tanner et al., 2016). For instance, individual academic schedules (academics or work) can be factored into their clinic visits. Personalized ART treatments are provided according to individual medical history and psychological support is provided individually (Mbalinda et al., 2021).

2.6.4 Education

This involves providing adequate teachings that facilitate understanding HIV and HIV-related challenges. Critical skills are taught and improvements are examined over time to ensure adolescents' knowledge of the skills and their progress documentation (Mbalinda et al., 2021). The adolescents are provided with this knowledge to be autonomous in their care which is much needed as they transition to adult care (Committee on Pediatric AIDS, 2013; Mbalinda et al., 2021).

2.6.5 Communication

Several transition studies have highlighted the importance of the free flow of communication between adolescents/pediatrics clinic staff and adult clinic staff in ensuring better retention in care after transition (Badejo et al., 2018; Biersteker et al., 2016). The communication could involve adolescents/pediatrics clinic staff intimating adult clinic staff on adolescents' medical histories (Biersteker et al., 2016; Tanner et al., 2016). The communication could also be between Adolescents on ART and adult clinic physicians (Biersteker et al., 2016; Tanner et al., 2016; 2018). This allows the familiarization of adolescents with the adult clinic staff, which is intended to mitigate the fear of transfer to adult clinics.

2.6.6 Support Groups

Support groups could come in form of peer groups and family support (Tanner et al., 2016; Masese et al., 2019). An example of a peer group could be a Teen Club. Masese et al. (2019)

posited that a Teen Club provided to adolescents and young adults in Tanzania helps foster bond and peer support which is crucial to navigating the transition process. The teen club runs on one Saturday monthly, giving opportunities for education sessions and socializing in addition to the routine clinic visits and pharmacy refills. The education sessions include seminars on nutrition, ART adherence and other health maintenance tactics. These sessions enhance bonding and peer support networks formation (Masese et al., 2019). Also, including celebrations and the presentation of transition certificates to adolescents in transition support groups, could enhance the successful transition of adolescents on ART to adult care (Tanner et al., 2016). Social supports, such as Parental/Familial support, may enhance perceived emotional social support and retention in care amongst adolescents on ART (Tassiopoulos et al., 2020). They also help adolescents deal with their HIV attributable social and emotional challenges (Biersteker et al., 2016).

2.6.7 Psychological support

Depression and depressive symptoms have been persistently associated with non-adherence, while high self-efficacy and low psychologic distress have been associated with improved adherence (Murphy, Wilson, Durako, Muenz & Belzer, 2001; Murphy et al., 2005; Naar-King et al., 2006; Williams et al., 2006). Hence, the need for psychological support in transition interventions.

2.6.8 Support for transition readiness

Transition support interventions should involve ongoing monitoring and evaluation to identify barriers of successful transition and mitigate same and this could lead to intervention adaption as required (Committee on Pediatric AIDS, 2013; New York State Department of Health AIDS Institute, 2016; Jones et al., 2019; Tanner et al., 2016). Evaluation could come in the form of readiness to transition assessment (readiness evaluation) (Jones et al., 2019; Ryscavage et al., 2016). Readiness evaluation exposes the patient's weakness in knowledge and skills so that suitable intervention to strengthen the identified aspects is provided (Jones et al., 2019; Mbalinda et al., 2021). The intervention provided could come in anticipatory guidance, education and/or skill training. Ryscavage et al. (2016) used a transition advocator to engage

patients in transition readiness a year before the actual transition. Hence, readiness evaluation takes time and is very important as the transition occurs when adolescents are deemed fit to transfer and not just according to age (Badejo et al., 2018). Follow-up (starting with an adolescent/pediatric staff following adolescents on their first visit to the adult clinic) should be conducted after transitioning to adult care (Badejo et al., 2018; Biersteker et al., 2016). Studies have posited that there should be a specific healthcare transition staff person within the adult clinic to ensure best practices and provide support to adolescents in their first year after transition (Biersteker et al., 2016; Tanner et al., 2018).

2.7 Chapter summary

In this chapter, I noted the outcomes of interest for adolescents on ART, namely, adherence to ART, retention in care and viral load suppression, as the measures of success for transition. Transition successes are assessed in the literature employing immunological, virological and behavioral markers. Transition interventions can be typed as pre-, during-, and post- transition interventions. The pre-transition interventions involved early disclosure of HIV status, support to accept disclosed state, introduction to and preparation for transition and assessment of transition readiness. The during-transition interventions involve HIV and health-related knowledge improvement, self-efficacy enhancement, independence promotion, coping tactics and psychological skills enhancement and further transition readiness assessment. The post-transition interventions involve transition staff support to get ALHIV adequately integrated into the adult clinic, assessing transition outcomes and experience to inform better strategies to transition ALHIV.

Transition support interventions identified in the literature include support for disclosure of HIV status, support from multidisciplinary/interprofessional teams, individualized care plan, education, communication, peer groups, family support, psychological support and support for transition readiness. As highlighted above, the chapter presents the available knowledge in the literature on transition interventions of ALHIV.

CHAPTER 3. METHODOLOGY

3.1 Study Design

The current study utilized a systematic review study design. A systematic review involves the systematic identification, selection and critical appraisal of relevant literature on a particular (health) intervention to synthesize available evidence which can give appropriate evidence-based knowledge on the intervention of interest and inform practices and policies in the best and right direction (Chandler et al., 2017). The study seeks to collate all up-to-date evidence that aligns with its eligibility criteria to address its specific review question. Hence, a systematic review study design is considered most appropriate. Furthermore, the steps involved in a systematic review are transparent, reliable, replicable, reduce bias and therefore produce the highest level of clinical evidence when properly conducted (Chandler & Hopewell, 2013).

In the current study, we aim to answer the review questions: what are the contents/strategies of transition interventions targeted at adolescents on ART and how effective are these transition interventions in improving adherence, retention in care and viral load suppression? A systematic review design offers a comprehensive, transparent and less biased review of available literature and it's ranked to be of better evidence quality than a literature review. Bias gets reduced by systematic identification, analysis, synthesis and (if possible) statistical aggregation in a systematic review (Muka et al., 2020). Hence, it is the study design that can offer the best answer to this question. Furthermore, utilizing a systematic review study design in this study helps inform researchers, clinicians and policy makers in right decision making and action taking regarding improving treatment outcomes for adolescents on ART.

3.2 Study protocol

The study protocol was registered with PROSPERO (“an international database of prospectively registered systematic reviews with health-related outcomes”) (REF: CRD42021273205) (Appendix A) to ensure transparency and authenticity. The study protocol was submitted for publication to BMC Systematic Reviews (Ref: SYSR-D-21-00837) (Appendix B). The study protocol developed was guided by Preferred Reporting Items stipulate for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. This PRISMA statement consists of a 27-item checklist and a four-phase flow diagram (Liberati et al., 2009).

The 27-item checklist constitutes sections such as topic, abstract, introduction, results, discussions and other information. According to the eligibility criteria, the checklist was adhered to for reporting and the four-phase flow diagram for screening studies.

This study adopts the eight steps to conduct systematic reviews advanced by Egger, Smith and Altman (2008) to guide this systematic review. The steps are: (1) formulate the review question; (2) define the inclusion and exclusion criteria; (3) develop a search strategy; (4) select study; (5) extract data; (6) assess studies quality; (7) analyze or synthesis the data and (8) interpret results.

3.3 Eligibility criteria

3.3.1 Inclusion criteria

The PICOT mnemonics standing for population, intervention, comparative, outcomes and time guided the definition of the inclusion criteria. My **P**opulation of interest was adolescents ages 10-19 years, living with HIV on Antiretroviral therapy. Any study that includes any part of these age range and fulfils other inclusion criteria will be included in this study. The reason for including such studies is to avoid selection bias and missing out on important information about the set population. The **I**ntervention of interest was transition interventions for adolescents on HIV treatment (ART). There was no **C**omparison as observational studies were included in this review. The primary **O**utcomes of interest were adherence to ART, retention in care, or viral load suppression. All secondary outcomes such as psychosocial wellbeing and self-efficacy were also considered. The **T**imeframe for the inclusion of published articles was 2000 to 2021. This timeframe was chosen because prior to the advent of and access to ARV pediatric HIV patients rarely make it to adolescent age. Hence, there was no need for transition intervention for adolescent on ART before the year 2000.

Grey literature and quantitative studies published in peer-reviewed journals in any language were considered. All languages were considered to avoid publication bias. Free online translation platforms were considered for translating published articles in other languages into English language.

3.3.2 Exclusion criteria

Literature reviews, protocols, systematic reviews and meta-analyses were excluded. Posters and background articles were excluded. Qualitative studies were excluded because they do not report quantitative outcomes of interest. Studies that did not describe the transition intervention but just mentioned transition in passing were excluded. Studies that did not report on the study outcomes were excluded.

3.4 Search strategies and information sources

The expertise of a librarian was sought to develop and modify the search strategy. Keywords such as HIV, "antiretroviral therapy," adolescents, pediatric, adult and "healthcare transition" were used to formulate the search strategies and adapted to the multiple databases specified in the protocol (Table 3.1). The search strategy used includes the following Boolean strings:

1. HIV OR AIDS OR "acquired immunodeficiency syndrome" OR "human immunodeficiency virus" OR "human immune-deficiency virus."
2. "Antiretroviral therapy" OR antiretroviral OR ART OR ARV OR HAART OR cART)
3. adolescents OR teenagers OR young adults OR teen OR youth OR student OR adolescence
4. paediatric OR pediatric OR child* OR "young person."
5. adult OR elderly
6. "Healthcare transition" OR transition OR transfer OR transferal OR transferring.

Multiple databases were searched to avoid missing relevant articles. These databases were PubMed, Scopus, Web of Science, Ebscohost, CINAHL, Science Direct and the World Health Organization's (WHO's) library database. Google Scholar search engine was equally searched to identify more relevant studies. Likewise, the reference lists of included studies were hand-searched to identify additional eligible studies. Also, some authors were contacted for clarification on transition processes and possible similar studies not yet published.

The reviewer searched the databases on 31 August 2021 and came up with a total of 1,009 identified studies that were exported to Mendeley software (table 3.2). After which, deduplication was performed and 406 studies were removed. Three additional studies were

added manually on searching references of the included studies, making the total number of identified studies 606. These 606 identified were screened for title and abstract. A breakdown of identified studies per database and deduplication is provided in.

3.3.3 Study selection

Two independent reviewers (OEJ & BVW) screened the title and abstracts of the studies identified according to the PICOT criteria. Full texts of the eligible studies were retrieved and reviewed by the two reviewers using Rayyan software and conflict of judgment between the two reviewers was resolved through discussion. Reasons for excluding studies at this stage were documented. The processes involved in the study selection were diagrammatically represented in the PRISMA flow chart in next chapter.

Table 3.1 Systematic review search strategy

Search criteria (based on PICO)	<p>Population: adolescents ages 10-19 years, living with HIV on Antiretroviral therapy.</p> <p>Intervention: transition interventions for adolescents on HIV treatment (ART).</p> <p>Comparison: Nil as observational studies will be included in this review.</p> <p>Outcomes: primary outcomes - adherence to ART, retention in care, or viral load suppression. Secondary outcomes: psychosocial wellbeing and self-efficacy.</p>
Search terms used for Scopus	TITLE-ABS-KEY (((hiv OR aids OR "acquired immunodeficiency syndrome" OR "human immunodeficiency virus" OR "human immune-deficiency virus") AND ("antiretroviral therapy" OR antiretroviral OR art OR arv OR haart OR cart) AND (adolescents OR teenagers OR young AND adults OR teen OR youth OR student OR adolescence) AND (paediatric OR pediatric OR child* OR "young person") AND (adult OR elderly) AND ("healthcare transition" OR transition OR transfer OR transferal OR transferring))))
Search terms used for Science Direct	HIV AND adolescent AND antiretroviral therapy AND paediatric AND adult AND healthcare transition AND transfer
Search terms used for PubMed, EBSCOHOST: Academic Search Complete, CINAHL Plus with Full Text and Web of Science Core	((HIV OR AIDS OR "acquired immunodeficiency syndrome" OR "human immunodeficiency virus" OR "human immune-deficiency virus") AND ("antiretroviral therapy" OR antiretroviral OR ART OR ARV OR HAART OR cART) AND (adolescents OR teenagers OR young adults OR teen OR youth OR student OR adolescence) AND (paediatric OR pediatric OR child* OR "young person") AND (adult OR elderly) AND ("healthcare transition" OR transition OR transfer OR transferral OR transferring))
Search terms used for Google Scholar	"Transition Interventions" and Adolescents AND "Antiretroviral Therapy" AND Transfer from Paediatric to Adult Healthcare
World Health Organization's (WHO's) library database	HIV AND antiretroviral therapy AND paediatric AND adult AND healthcare transition
Limiters	Timespan - 2000-2021, Adolescents – 10-19 years

Table 3.2 Summary of identified studies and deduplication

PubMed	244
Scopus	212
Web of Science	161
Ebscohost [Academic Search Complete]	118
CINAHL	53
Science Direct	188
Google Scholar	28
World Health Organisations Library	5
Manually added	3
Total number of identified articles	1012
Deduplication	406
Total identified studies for the title and abstract screening	606

3.5 Selection process

3.5.1 Title and abstract screening

Using the PICOT criteria, two researchers independently screened the identified studies (N=606) for eligibility. The result of these screenings led to the exclusion of 552 identified studies. After the title and abstract screening, 54 studies were potentially eligible (figure 4.1).

3.5.2 Full-text screening

The 54 identified studies and their full texts were exported to Rayyan software. The two reviewers independently screened the full text of the 54 identified studies on Rayyan and conflicts of judgment were resolved through discussion. Overall, 47 included studies were further excluded. The reasons for exclusion include “not an outcome of interest” (1), studies being “posters” (2) and largely “not transition intervention” (44). Seven studies met all the eligibility criteria and were included in the narrative synthesis.

3.6 Data extraction

A data extraction form was designed and piloted to gather information on the author, year of publication, country, study population (sample size), study design/outcome, description of the intervention, outcomes and result. This form helped synthesize relevant information from the individual studies standard and transparently. Two independent reviewers (OEJ & BVW) extracted the data. The information extracted is presented in a table clearly and concisely. Microsoft Excel software application was used to organize the data extraction form.

3.7 Critical appraisal of studies

The National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies was suitable for this review (Appendix D). The reason is that the studies included in this review are only cohort and cross-sectional in design as the search did not yield any randomized controlled trials. The tool deployed in this study comprises fourteen questions used to detect flaws in study methods or implementation, sources of bias, confounding, study power, the strength of causality and other factors. Each question/item in the tool could be answered on a three-point item code of “Yes = no potential bias or flaws,” “No = presence of bias or flaws” while “Cannot Determine” and “Not Reported” = potential flaws (Risk assessment workgroup, 2013). The collated answers from the fourteen questions produce the study's overall quality. The quality rating of a study can be judged to be either “Good,” “Fair,” or “Poor.” “**Good**” quality rating implies a low risk of bias, “**fair**” quality rating implies a moderate risk of bias and “**poor**” quality rating implies a high risk of bias. This National Institutes of Health (NIH) quality assessment tool has been effectively used in recent systematic reviews involving observational studies only (Aasa, Svartholm, Andersson & Berglund, 2017; Inoue et al., 2020). Hence, its effectiveness has laid credence to the choice of its use for this review. Studies were rated poor quality if exposure and/or outcome measurements were not clearly defined and confounding variables were not adjusted statistically.

3.8 Ethics considerations

Approval to conduct the study was obtained from the Biomedical Research Ethics Committee of the University of the Western Cape (REF. BM21/9/5) (Appendix C). The systematic review involved a secondary analysis of published and grey literature already in the public domain; therefore, there were no consent issues.

3.9 Chapter summary

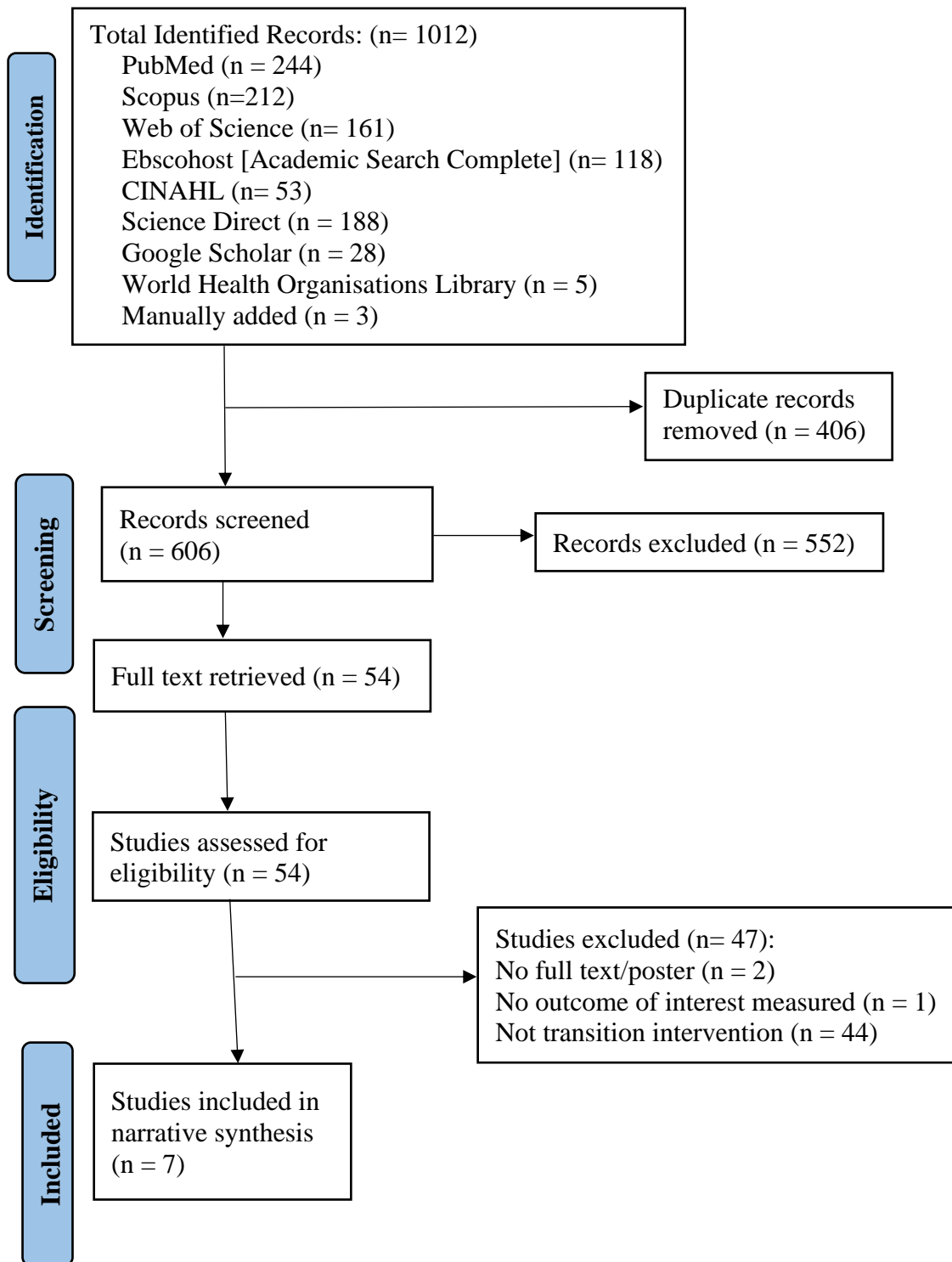
This chapter has presented the steps and processes involved in conducting this review in detail, section by section. The next chapter will present the findings of this review.

CHAPTER 4: RESULTS

4.1 Results of literature search

A PRISMA flow diagram (Figure 4.1) shows the diagrammatic presentation of the processes followed in achieving the seven included studies for narrative synthesis. We identified 1,009 studies from the search of Seven databases (PubMed, Scopus, Web of Science, Ebscohost, CINAHL, Science Direct and the World Health Organization's (WHO's) library) and (Google scholar). Three additional studies were added manually by searching references of the included studies. In total, 1,012 studies were identified. Deduplication led to the exclusion of 406 studies and 606 studies went through title and abstract screening. After which, 552 studies were excluded while the remaining 54 studies went through full-text screening. The 552 studies were excluded because their titles and abstract failed to meet the stated PICOT criteria for the study. After the full-text screening, 47 additional studies were excluded because they did not meet the eligibility criteria. Only seven studies met the eligibility criteria and all were included in the narrative synthesis. A meta-analysis could not be carried out due to data heterogeneity. One study was written in Swedish and translated to English using a free online translation platform (Systran).

Figure 4.1 Prisma flow diagram for the review



4.2 Characteristics of included studies

The characteristics of the seven included studies are summarized in Table 4.1 below. The year of publication of included studies ranged from 2014 to 2020. Most studies (n=5) were conducted in high-income countries: two in Italy and the United States of America and one in Sweden. The remaining two studies were conducted in Thailand, an upper-middle-income country (World Bank Country and Lending Groups, 2022).

Five studies used a cohort study design (Lolekha et al., 2017; Continisio et al., 2020; Griffith et al., 2019, Maturo et al., 2015; Hansudewechakul et al., 2015) and two were cross-sectional surveys (Righetti et al., 2015; Westling et al., 2014). The sample sizes ranged from small (13) to moderate sample size (192).

The duration of the transition interventions ranges from six months to ten years. Except for Continisio et al., 2020 and Lolekha et al., 2017 which measured outcomes at baseline, 12 months, and 18 months, all other studies employed a one-time point outcomes measurement. Also, only Hansudewechakul et al., 2015 and Righetti et al., 2015 measured outcomes on a long-term basis at six years and ten years, respectively. Other studies measured outcomes on a short-term basis between six and twenty-four months.

Table 4.1 Characteristics of the included studies

First Author, year	Country	Study population, (Sample size)	Study design	Description of Intervention	Outcomes	Results
Righetti, 2015	Italy	Children and Adolescents (2-18 years) N = 45 [2 - 9 years: n = 25 10 -18 years: n = 20]	Cross-sectional survey	<ul style="list-style-type: none"> • Interprofessional team provide an individualized care plan for patients • Child-customized environment • A meeting between patients/caregivers and adult providers before the transition • Psychological support for patients and families • Health and sexual education • Education for increased cART adherence (all education is part of transition intervention) 	Retention in care (at 10 years)	84.4% (38/45)
					Adherence (of those retained in care)	92.1% (35/38)
					Viral load suppression (of those who adhered)	91.4 (32/35)
					In total participant <50copies/ml	71.1% (32/45)
					Secondary outcome	
					Self-efficacy	79.0% (30/38)
Griffith, 2019	United States	Young adults (18-30 years) N = 137 [Accessing Care Early (ACE): n = 61 Standard of Care (SOC):	Retrospective cohort	<ul style="list-style-type: none"> • Youth-focused care • Weekly review of patients by a multidisciplinary team • Appointment reminders from the peer navigator. 	Primary outcomes Retention in care (At 24 months)	18 transferred out or moved (10 ACE and 8 SOC) ACE vs. SOC: 49% vs. 26%, p<0.001

		n =76]		<ul style="list-style-type: none"> • Variable appointment times and schedules. 		(25/51 vs. 18/68)
					Virologic suppression (At 24 months)	For those who were retained: ACE vs. SOC: 60% (15/25) vs. 89% (16/18) (P=0.04)
Maturo, 2015	United States	Adolescents and young adults (14-23 years) N = 38	Retrospective cohort	<ul style="list-style-type: none"> • Preparation for transition with special adolescent clinic (SAC) team. • Communication between SAC and adult care physician • Familiarization of clients with the adult care physician both at the SAC and adult clinic • One-year follow-up after the transition <p>[SAC provides individual/group therapy, client education, peer counseling]</p>	Retention in care (At 12 months)	55% (21/38)

Lolekha, 2017	Thailand	Youth (14-22 years) N = 192	Prospective cohort	<ul style="list-style-type: none"> • One-day weekend workshop • Two half-day meetings • Three individual sessions over 18 months 	Retention in care (At 18 months)	84% (161/192)
						83% (134/161)
					Retention in care (at 12 months post-intervention)	
Continisiso, 2020	Italy	Adolescents (13-20 years) N = 13	Prospective cohort	<ul style="list-style-type: none"> • Joint pediatric/adult transition clinic running every two months • Education session • Psychological support - once a month • Group discussion with patients and their families twice a year • Simplification of ART therapy 	Adherence (>95%) (At 18 months) for those retained in care	70% (159/192)
						99% (159/161)
					Retention in Care (At 18 months)	92% (12/13)
					Viral load suppression (At 18 months)	92% (12/13)
					Secondary outcomes:	
					•Psychological general wellbeing	
					•Self-esteem	

Westling, 2014	Sweden	Young people (17-25 years) N = 34	Cross-sectional survey	<ul style="list-style-type: none"> • A monthly transfer reception run with a visit every three months per patient in the evenings. • care adapted to individual needs • Sex and cohabitation counseling • adherence to treatment education 	Adherence (At six months)	88% (30/34)
					Viral load suppression (< 50 copies/ml) (At 6 months)	79% (27/34)
Hansudewechakul, 2015	Thailand	Adolescents (11-18 years) N = 67	Prospective cohort	<ul style="list-style-type: none"> • A group transition program • 1 - 2 days transition camp • Communication between adolescents and adult HIV care providers • Introduction of adolescents to different sections of the adult clinic • Transferred as a group after camp. 	Retention in care (At six years)	73% (49/67)
					Viral load <40copies/ml (at 6 years)	76% (37/67)

4.3 Risk of Bias and Quality Assessment of Studies

Table 4.2 summarizes the results from the assessment of risk of bias and quality for all included studies based on the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies. This tool consists of 14 items. These items were scored for each included study and classified as “good,” “fair,” or “poor.” For a study to be rated “good,” it has to be positive for at least eleven of the items and for “fair,” nine of the items, while for “poor,” eight of the items and below. This classification helped to factor in different bias judgments for the included studies. Three studies (Griffith et al., 2017; Lolekha et al., 2017; Continisio et al., 2020) were rated *good quality*, which is equivalent to a *low* risk of bias. Confounding was controlled for in these studies except for Continisio et al. (2020) (the only question receiving a “no” in this study). One study (Maturo et al., 2015) was rated *fair quality*, equivalent to *moderate* risk of bias. It fulfilled nine items cut-off point for *fair*, which highlighted that its participation rate was less than 50% and confounding was not controlled for. The other three studies (Righetti et al., 2015; Westling et al., 2014; Hansudewechakul et al., 2015) were rated *poor quality* equivalent to a *high* risk of bias. This is because they had positive eight items and below, which highlighted that exposure and/or outcome measures were not defined, sample sizes were not justified, no effect estimates and confounding variables were not adjusted statistically.

Table 4.2 Risk of Bias and Quality Assessment of included studies

Criteria	Righetti	Griffith	Maturo	Lolekha	Continisio	Westling	Hansudewechakul
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y	N
2. Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y
3. Was the participation rate of eligible persons at least 50%?	Y	Y	N	Y	Y	Y	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y	Y	Y	Y	Y
5. Was a sample size justification, power description, or variance and effect estimates provided?	N	Y	Y	Y	Y	N	N
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	N	Y	Y	Y	Y	N	Y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	N	Y	Y	Y	Y	Y	Y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	NA	NA	NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable and implemented consistently across all study participants?	NA	Y	Y	Y	Y	Y	Y
10. Was the exposure(s) assessed more than once over time?	NA	NA	NA	Y	Y	N	N
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable and implemented consistently across all study participants?	N	Y	Y	Y	Y	Y	N
12. Were the outcome assessors blinded to the exposure status of participants?	N	NA	N	N	Y	N	N
13. Was loss to follow-up after baseline 20% or less?	Y	Y	Y	Y	Y	Y	Y
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	N	Y	N	Y	N	N	N
Over-all Quality rating	Poor	Good	Fair	Good	Good	Poor	Poor

CD, Cannot determine; N, No; NA, not applicable; Y, Yes.

4.4 Transition Interventions

The transition interventions can be grouped as pre-, during- and post-transition. One study focused solely on pre-transition, three focused on during-transition, and the remaining three incorporated pre-, during- and post-transition interventions. In this review, no study focused solely on post-transition intervention.

4.4.1 Pre-Transition Intervention

Lolekha et al. (2017) is the only study in this review that focused solely on pre-transition intervention. The intervention prepared older adolescents ages 14 to 22 years for the transition by exposing them to HIV and health-related knowledge, which can bring about positive health outcomes during and after their transition to adult healthcare.

4.4.2 During-Transition Intervention

Three studies focused solely on during-transition intervention (Westling et al., 2014; Griffith et al., 2019). Westling et al. (2014) implemented a *transition reception* that was neither for pediatrics nor adults but HIV-positive adolescents preparing to transition into adult care. This reception runs every month, but the appointment is every three months per patient. At first, adolescents received care from the multidisciplinary staff at the reception and then later, they received care from both the reception personnel and the adult healthcare personnel. The transfer reception provided them with individualized care according to their need and allowed them to consult a sexologist regarding their concerns about their sexuality.

Griffith et al. (2019) assessed a youth-focused transition intervention – *Access Early Care (ACE)* compared to the Standard of Care (SOC). The ACE served as a transition clinic for those with a high risk of attrition and viremia. They have been exposed to additional phone or text message bi-directional communication from their peer navigator and care from four physicians with combined internal medicine and pediatric training.

For Hansudewechakul et al. (2015), the during-transition intervention consisted of interdepartmental case conferences that involved pediatric and adult clinic staff, hospital home

care team and clinical psychologist consultants. The adolescents were involved in a transition camp that focuses on antiretroviral management, HIV transmission and navigating adult HIV care settings. The study also involved a group transition system that ensures the adolescent cohort gets an initial appointment and appointment to present at the adult clinic together. Coupled with this is the presence of a pediatric provider in their first few appointments at the adult clinic to ensure proper integration through the provision of immediate support and answers to questions.

4.4.3 Post Transition Intervention

This type of transition intervention occurs in the adult clinics and focuses on assessing treatment outcomes after the transition has occurred. This is implemented to inform better strategies to transition ALHIV and examine if the transition was successful or not (Hussen, Chahroudi, Boylan & Andres, 2014). Three studies (Continisio et al., 2020, Maturo et al., 2015 and Righetti et al., 2015) incorporated this intervention alongside other types of transition interventions.

4.4.4 Combination interventions

Three studies (Continisio et al., 2020, Maturo et al., 2015 and Righetti et al., 2015) incorporated all three stages of transition intervention.

For Continisio et al. (2020), the pre-transition intervention involved complete clinical, immunological and virological evaluations. Information on disease knowledge, adherence to therapy and psychological status (including self-esteem) were gathered from adolescents who already knew their HIV status. The during-transition phase involved a joint medical visit run by a multidisciplinary team involving pediatric and adult clinic physicians every two months. The visits were partly done at the adult clinic in the presence of pediatric staff. The interventions at this stage also involved 30 to 60 minutes of education sessions with each patient at the pediatric clinic. Psychological support-oriented individual meetings were conducted by a psychologist monthly and group discussion that involved adolescents and their families twice a year. A nurse and a gynecologist provided information on HIV transmission prevention and ways to protect themselves in the advent of sexual activity.

The post-transition interventions included adolescents' clinical evaluation, HIV immunological class, CD4+ count and percentage and HIV viral load assessments. The interventions also included administering the Psychological General Well-Being (PGWB) questionnaire and psychological follow-up.

Maturo et al. (2015) piloted a transition protocol covering pre-, during and post-transition interventions in five different phases. For the pre-transition intervention, the study focused on discussions with adolescents on the need to transition to adult care and the introduction of adolescents to the adult physician at the special adolescent clinic. The during-transition intervention involved adolescents being cared for at the special adolescent clinic by the adult physician, followed by their first appointment at the adult clinic in which the same adult physician attended to them. The post-transition intervention is an evaluation process that happens one year after transition in a follow-up appointment conducted by the special clinic adolescent Social Worker and Peer Advocate. After that, their judgment is conveyed to both the special adolescent clinic team and adult infectious disease physicians to improve the process.

For Righetti et al. (2015), the pre-transition intervention involved an interprofessional team providing an individualized care plan for patients one day a week, a meeting between patients/caregivers and adult providers before the transition and psychological support for patients and families. The during-transition intervention involved health and sexual education interventions for increased independent medication management and cART adherence during follow-up and education programs. The post-transition intervention involved a survey investigating the efficacy and quality of the transition to adult care and implementing further follow-up.

4.5 Components of transition interventions

Six components of transition interventions were focused on across the included studies. These are individualized care plan, group transition program, communication, psychological support, health and sexual education and mHealth.

4.5.1 Individualized care plan

The majority (six of seven) of the transition intervention focused on providing care, support, education and counseling to individual adolescents. This was implemented in variable appointments or times to suit individuals, tailored antiretroviral treatment to meet individual needs, individualized counseling, therapy or sessions.

4.5.2 Group Transition Program

Only one transition intervention focused on transitioning adolescents as a group (Hansudewechakul et al., 2015). This involved a camp meeting that accommodates interaction between adolescents and adult clinic healthcare professionals and their peers. After which, transition takes place as a group. The adolescents' first appointment in the adult clinic will be a group appointment. This was done to provide peer support and proper integration during the transition.

4.5.3 Communication

Steady flow of communication between patients/pediatric or adolescent healthcare givers and the adult clinic specialists were emphasized in four studies (Continisio et al., 2020; Hansudewechakul et al., 2015; Lolekha et al., 2017; Righetti et al., 2015). This was noted to give adolescents a voice in the programs and enhance the efficient transitioning process between pediatric/adolescent clinic staff and the adult clinic staff.

4.5.4 Psychological support

Three studies (Continisio et al., 2020; Lolekha et al., 2017; Righetti et al., 2015) incorporated psychological support for adolescents and their families in their approach to effective transition from pediatric to adult health care. Righetti et al. (2015) provided psychological support by meeting needs associated with diagnosis disclosure, HIV acceptance, the weight of living with a chronic disease and demanding family structures or dynamics. Continisio et al. (2020) on the other hand, supported psychologically by conducting an individual meeting once a month by a psychologist knowledgeable in pediatric HIV infection management to adolescents. Also, group meetings were conducted with all adolescents and their families twice a year. Lolekha et al. (2017)

utilized 30–60 min individual sessions that allowed counselors to provide psychological support to HIV-positive youth.

4.5.5 Health and sexual education

Six studies implemented health and sexual education in their transition approach (Continisio et al., 2020; Hansudewechakul et al., 2015; Lolekha et al., 2017; Maturo et al., 2015; Righetti et al., 2015; Westling et al., 2014). Continisio et al. (2020) provided “a 30- to 60-min face-to-face education session focusing on HIV infection, its clinical manifestations, risks, transmission routes and prevention measures and principles of ART and adherence to each patient”. Hansudewechakul et al. (2015) utilized a transition camp to educate on antiretroviral management, the transmission of HIV and piloting adult HIV care settings. Lolekha et al. (2017) used a sexual education and risk reduction counseling approach which focused on safe sex behaviors, relationships, reproductive health, family planning and healthy conception, reducing risk behaviors for HIV and STIs and HIV-disclosure and partner testing. In addition, Lolekha et al. (2017) provided health knowledge on transitioning to adult HIV care, self-care (e.g., ART adherence, keeping appointments) and knowledge about Health Care Insurance.

Maturo et al. (2015) incorporated health and sexual education by providing client education and peer counseling.

Righetti et al. (2015) focused its health and sexual education on reducing risk behaviors for HIV transmission, increasing positive lifestyle and increasing independent management of medications to increase cART adherence. Westling et al. (2014) employed the services of a sexologist who helps to deal with adolescents’ concerns about their sexuality, sex and cohabitation. This approach ensures they practice safe sex and avoid HIV transmission to their partners (though it was noted that not many of them were sexually active). They were also giving education on contraceptive use.

4.5.6 mHealth intervention

Griffith et al. (2019) compared transition treatment outcomes between adolescents receiving Access Care Early (ACE) transition program and those receiving Standard of Care (SOC). In

addition to the automated appointment reminders received by SOC, all ACE patients received phone or text message bi-directional communication from their peer navigator. “Bidirectional communication with the peer navigator was defined as a telephone or electronic message conversation between the patient and the peer navigator. The unidirectional conversation was defined as a telephone or electronic message left by the peer navigator without documented patient response to the message” (Griffith et al., 2019). A significant association was reported between retention in care and frequent social work visits, nurse phone calls and peer navigator interactions. More ACE patients were retained in care compared with SOC patients.

4.6 Outcomes of Transition interventions

All studies included in this review except Maturo et al. (2015) reported on more than one outcome of interest. Six studies reported retention in care; three reported adherence, while four reported viral load suppression.

4.6.1 Retention in care

Six out of the seven studies reported retention in care. Most of the studies (Continisio et al., 2020; Hansudewechakul et al., 2015; Lolekha et al., 2017; Maturo et al., 2015; Righeti et al., 2015) measured retention in care as a percentage of adolescents still in care, excluding those lost to follow up, those who died and those transferred or moved out. Only one (Griffith et al., 2019) used a standard definition for retention measurement, which is the United States Health and Human Services Health Resources and Services Administration (HRSA) HIV/AIDS Bureau Performance Measure for HIV medical visit frequency measured as “at least one medical visit in each 6-month period of a 24-month period with a minimum of 60 days between the first medical visit in the prior 6-month period and the last medical visit in the subsequent 6-month periods”. Also, ACE participants included in Griffith et al., 2019 have a high risk of attrition and viremia. The time point for retention in care ranges from 1-year (Maturo et al., 2015) to 10 years (Righetti et al., 2015). The percentage retention in care spans 49% in Griffith et al. (2019) at two years to 92% in Continisio et al. (2020) at one year six months.

4.6.2 Adherence

Of the seven studies, three reported adherence to antiretroviral therapy. These studies include Righetti et al. (2015); Lolekha et al. (2017); Westling et al. (2014). The percentage of patients who adhered to treatment was 92%, 99% and 88%.

4.6.3 Viral load suppression

Four studies reported viral load suppression: Griffith et al. (2019); Continisio et al. (2020); Westling et al. (2014); Hansudewechakul et al. (2015). Viral load was measured in copies/ml. Variable definitions were used to measure viral load suppression in the studies. Continisio et al. (2020) and Hansudewechakul et al. (2015) measured viral load suppression at <40 copies/ml. Westling et al. (2014) measured it as <50 copies/ml, while Griffith et al. (2019) measured it at <200 copies/ml. The percentage of virologically suppressed patients ranged from 60% in Griffith et al. (2019), to 92% in Continisio et al. (2020).

4.6.4 Secondary Outcomes

Psychosocial wellbeing and self-efficacy were reported in only two [Continisio et al. (2020) and Righetti et al. (2015)] of the included studies.

Continisio et al. (2020) measured general psychological wellbeing using the Psychological General Well-Being (PGWB) index and self-esteem using The Multidimensional Self-Esteem Test (TMA). While psychological wellbeing increased in adolescents, there was no significant increase in self-esteem.

Righetti et al. (2015) reported self-efficacy concerning patients' ability to manage their medication independently. Thirty out of 38 (79%) were able to manage their medication without anyone's assistance.

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1 Introduction

This chapter serves as the final chapter of this systematic review. It discusses the main findings, highlights the limitations and provides targeted recommendations for transition interventions focusing on adolescents on ART to ensure better treatment outcomes.

5.2 Main findings

This section discusses the main findings in this review: the scope and quality of interventions (number of included studies, sample sizes, study designs and differentiated care), the effectiveness of the six components of transition interventions across included studies, and high-income bias.

5.2.1 Scope and quality of interventions

This review found few transition intervention studies that have been formally evaluated. Even though several studies described transition interventions, they did not evaluate the outcomes. In other studies, no transition interventions were implemented before the treatment outcomes were measured. Hence, they were excluded from this review.

All the included studies had sample sizes that fall within the small to moderate size range. Small sample sizes have large variations and are prone to an inaccurate estimate of the true effect size (Faber & Fonseca, 2014). This issue could lead to the non-generalizability of the findings to other settings. In addition, reliability regarding intervention efficacy could also be hampered.

The current review found no randomized control trials (RCTs) to evaluate the effectiveness of transition interventions for adolescents on ART on treatment outcomes. Generally, randomized control trials with adequate sample size and appropriate blinding are widely regarded as providing the highest level of evidence in epidemiological studies (Wingo, Higgins, Rubin, Zahniser & Centers for Disease Control, 1994; Zabor, Kaizer & Hobbs, 2020). Well-designed RCTs have fewer systematic errors and biases than observational studies such as cross-sectional surveys and

retrospective cohorts (Burns, Rohrich & Chung, 2011). Randomization also helps prevent biases, minimize confounding, produce comparable intervention groups and ensure a higher level of result reliability (Suresh, 2011). Therefore, it is strongly recommended that future transition research involve rigorous designs (such as RCTs) to measure the effects of interventions on treatment outcomes for adolescents on ART.

All transition interventions included in the current review were conducted in healthcare facilities. No community-based transition interventions have focused on adolescents on ART. This poses a window of opportunity for HIV transmission, especially among adolescents living in underserved areas with little or no access to healthcare facilities. Differentiated care, such as community adherence groups in Mozambique, can be extended to adolescents on ART in underserved areas (Decroo et al., 2014). A community-based transition intervention can help alleviate the heightened stigma adolescents experience at this developmental stage of their lives (Cabal, 2017). Extending interventions beyond the health system could be a possible solution to the social determinants of health, particularly for adolescents on ART (Biersteker et al., 2016).

This review's transition interventions studies involved both perinatally infected and behaviorally infected adolescents. However, most of the studies mainly focused on perinatally-infected adolescents. There are concerns with using the same intervention for behaviorally and perinatally infected adolescents. Hence, some studies have recommended that behaviorally infected adolescents be researched (Maturo et al., 2015).

5.2.2 Effectiveness of the six components of transition interventions

Transition interventions across studies are heterogeneous and differentiated care is provided (Jones et al., 2019). Six components of these heterogeneous and differentiated care were highlighted across the included studies in this review. These are individualized care plans, group transition programs, communication, psychological support, health and sexual education and mHealth. All studies in this review use an interprofessional/multidisciplinary team, even though the teams'

professionals differ across studies. For *individualized care plan*, it includes considering working hours for employed adolescents, school hours for those attending schools, individual transition readiness to transfer for all adolescents, individualized counseling sessions, personalized ART treatments provided according to individual medical history and personalized psychological support (Hansudewechakul et al., 2015; Maturo et al., 2015; Westling et al., 2014). This approach effectively improved adherence, retention in care, and viral load suppression in almost all the studies at post-transition over the short and long term.

For *group transition program* - this is a program in which adolescents are transferred to the adult clinic as a group to provide peer support, which can lead to better treatment outcomes among each group. Hansudewechakul et al. (2015) reported that the approach was very effective and successfully provided technical support to sixteen other locations. However, the quality of evidence was weak. Hence, there is a need for rigorous evaluation designs to measure the effects of group transition on treatment outcomes for adolescents on ART.

For *communication* – free flow of communication between sending and receiving health staff and between adolescents and receiving health staff has proven effective. These ensured proper management of each adolescent on ART at both clinics and helped them familiarize themselves with receiving health staff, easing their transition fears. This intervention has improved adherence, retention in care, and viral load suppression post-transition over the short and long term.

For *psychological support* – this involves the expertise of psychologists knowledgeable in pediatrics HIV. The health staff meet the needs of adolescents during HIV disclosure, supporting them to accept their HIV status, helping them navigate demanding family dynamics, and providing one-on-one sessions with adolescents on ART and their family members to combat mental situations such as depression or its symptoms. This has been shown to improve self-efficacy and promote low psychologic distress among adolescents on ART, leading to better treatment outcomes. Psychological support has been effective in improving adherence, retention-in-care, and viral load suppression post-transition over the short and long term.

For *health and sexual education* – this involves educating adolescents on HIV infection, its clinical manifestations, risks, transmission routes and prevention measures, principles and management of ART, safe sex behaviors, relationships and partner testing, reproductive health and family planning. Peer counseling can be used to educate adolescents. A sexologist can also be employed

to deal with concerns about adolescents' sexuality. This approach was found effective in improving adherence, retention in care and viral load suppression.

For mHealth intervention involves using telecommunication devices for adolescents' appointment reminders. This could be in the form of phone or text message communication that is bi-directional from a peer navigator in addition to the automated appointment reminders. This was found effective in improving retention in care and viral load suppression post-transition over the short and long term.

5.2.3 High-income settings bias

There is a lack of sub-Saharan African studies evaluating transition interventions for adolescents on ART. This is quite worrisome and concerning because most countries with the highest adolescents living with HIV are in sub-Saharan Africa (Badejo et al., 2018). This paucity in research could be attributed to the lack of national and clinical guidelines and protocols in most sub-Saharan Africa (Dahourou et al., 2017). Also, Njuguna et al. (2019) reported that validated tools for assessing transition interventions among adolescents on ART are lacking in sub-Saharan Africa. There is a need for strategic support in sub-Saharan Africa to develop national guidelines and protocols focused on adolescents' transition (pre-, during- and post-) from pediatric/adolescent clinics to adult care.

5.3 Recommendations for clinical practice

The included studies show that transition interventions that integrate individualized care, communication between sending and receiving staff and between adolescents and receiving staff, psychological support, health and sexual education and a mHealth approach can improve treatment outcomes among adolescents on ART. The findings of this review can be utilized by health providers involved with ALHIV's care to develop and implement transition guidelines that have been proven to support positive treatment outcomes among adolescents on ART. A multidisciplinary/interpersonal team needs to be formed to develop the transition guidelines. This team will help develop and implement the transition guidelines. The transition guidelines should

first focus on an individualized care plan by considering the different realities experienced by adolescents on ART. Second, the transition guidelines should provide a robust communication and client data sharing system between the clinics and strategic familiarization and integration of clients with the adult clinic. Third, a psychological support structure should be built into the guidelines. This will particularly help identify adolescents struggling to transition and enable specific transition interventions can be provided to them according to need. Four, health and sexual education should start early pre-transition and continue throughout the transition process. Five, a mHealth approach such as appointment reminders and communication exchange between adolescents and their health providers, such as peer navigators, should be clearly stated and provided in the guidelines. Lastly, monitoring and evaluation should be incorporated into the guidelines throughout the transition process to give room for reviews and adjustments as needed.

5.4 Recommendations for further research

This review has filled a gap in the literature by describing available transition interventions, their quality of evidence and highlighting what works for transitioning adolescents on ART from pediatric/adolescent to adult clinics. This review has also revealed an absence of quantitative research on this topic in sub-Saharan Africa settings where adolescents on ART are predominantly domiciled and health resources are most scarce. This calls for more studies on transition interventions and their effectiveness evaluation within the sub-Saharan Africa settings. There is also a lack of transition policies and protocols at national and clinical levels in sub-Saharan Africa. More concerted research efforts should be put in place to develop transition policies and protocols that are tailored to suit sub-Saharan African countries. Available studies are poorly powered because of their small sample sizes and there is no study using randomized control trials. Hence, better-powered studies and trials are needed to evaluate the effectiveness of transition interventions focused on adolescents on ART. These studies will generate high-level evidence that can be used to determine the effectiveness of interventions with a minimal level of bias.

5.5 Limitations

The paucity of published literature describing transition intervention focused on adolescents on ART in this review is its main limitation. Also, the small sample sizes of the included studies make it difficult to determine the effectiveness of interventions. Although seven databases and one search engine were consulted using aligning search strategies, there could be omissions of unpublished studies and studies that were not correctly indexed, leading to the identification of fewer studies.

5.6 Conclusions

This systematic review has described the few available transition interventions targeted at adolescents on ART. It has compiled interventions that successfully transition adolescents from pediatric to adult clinics in different settings. These interventions include individualized care plan, group transition, communication between the pediatric and adult clinic and between adolescents and adult clinic staff, psychological support (clinical, family and peer), health and sexual education and mHealth. Based on the strength of evidence of the included studies, we strongly recommend transition interventions that include a combination of individualized care, communication between sending and receiving staff, psychological support, health and sexual education and a mHealth approach to improve treatment outcomes among adolescents on ART. We also recommend familiarization of adolescents on antiretroviral therapy with adult care physicians both at the sending and receiving clinics. We recommend further research with rigorous evaluation designs to measure the effects of group transition on treatment outcomes for adolescents on antiretroviral therapy.

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Appendix A

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided [here](#).

Citation

Olubukola Esther Jegede, Brian Van Wyk. Transition Interventions for Adolescents on Antiretroviral Therapy on Transfer from Pediatric to Adult Healthcare: A Systematic Review. PROSPERO 2021 CRD42021273205 Available from: https://www.crd.york.ac.uk/prospéro/display_record.php?ID=CRD42021273205

Review question

What are the effects of transition interventions to improve health outcomes among adolescents living with HIV transitioning from pediatric to adult healthcare?

Searches

PubMed, Cochrane Library, CINAHL, Scopus, ScienceDirect, Web of Science, JSTOR, PsycINFO, Google Scholar, and the World Health Organization's (WHO's) library database.

No language restriction but publication date for included studies will be from the year 2000 to 2021.

Types of study to be included

There are no restrictions on the study types for this review.

Condition or domain being studied

The area being studied is to describe and synthesize evidence on the effects of transition interventions to improve health outcomes among adolescents living with HIV on antiretroviral therapy transitioning from pediatric to adult healthcare

Participants/population

Inclusion Criteria

Population being studied are adolescents ages 10-19 years, living with HIV on Antiretroviral therapy.

Exclusion Criteria

Adolescents who are not HIV positive

Adolescents living with HIV on Antiretroviral therapy that are not transitioning to adult healthcare

Intervention(s), exposure(s)

Inclusion criteria

Transition Interventions focused on transfer from pediatric/adolescent clinics to adult care

Exclusion criteria


Interventions on improving health outcomes among adolescents that are not focused on their transitioning to adult care

Comparator(s)/control

Not relevant

Appendix B

12/6/21, 10:10 PM Gmail - Confirmation of your submission to Systematic Reviews SYSR-D-21-00837 - [EMID:2251d8ae4af999dd]

 bukola jegede <bukolajegede.bj@gmail.com>

Confirmation of your submission to Systematic Reviews SYSR-D-21-00837 - [EMID:2251d8ae4af999dd]
2 messages

Systematic Reviews Editorial Office <em@editorialmanager.com> Fri, Sep 3, 2021 at 9:37 PM
Reply-To: Systematic Reviews Editorial Office <judy.maturan@springer.com>
To: Olubukola Esther Jegede <bukolajegede.bj@gmail.com>

SYSR-D-21-00837
Transition Interventions for Adolescents on Antiretroviral Therapy on Transfer from Pediatric to Adult Healthcare: A Systematic Review Protocol.
Olubukola Esther Jegede; Brian Van Wyk
Systematic Reviews

Dear Mrs Jegede,

Thank you for submitting your manuscript "Transition Interventions for Adolescents on Antiretroviral Therapy on Transfer from Pediatric to Adult Healthcare: A Systematic Review Protocol." to Systematic Reviews.

The submission id is: SYSR-D-21-00837
Please refer to this number in any future correspondence.

During the review process, you can keep track of the status of your manuscript by accessing the following website:

<https://www.editorialmanager.com/sysr/>

If you have forgotten your username or password please use the "Send Login Details" link to get your login information. For security reasons, your password will be reset.

Best wishes,
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Systematic Reviews
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****Our flexible approach during the COVID-19 pandemic****

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

Recipients of this email are registered users within the Editorial Manager database for this journal. We will keep your information on file to use in the process of submitting, evaluating and publishing a manuscript. For more information on how we use your personal details please see our privacy policy at <https://mail.google.com/mail/u/0/?ik=dc2e038fc1&view=pt&search=all&permthid=thread-f%3A1709910617655501602&simpl=msg-f%3A1709910617655501602&simpl=msg-a%3A304786152419634677> 1/2

Appendix C



UNIVERSITY of the
WESTERN CAPE



29 October 2021

Mrs OE Jegede
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM21/9/5

Project Title: Transition Interventions for Adolescents on Antiretroviral Therapy on Transfer from Pediatric to Adult Healthcare: A Systematic Review.

Approval Period: 22 October 2021 – 22 October 2024

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project and the requested amendment to the project.

Any further amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report annually by 30 November for the duration of the project.

For permission to conduct research using student and/or staff data or to distribute research surveys/questionnaires please apply via:
<https://sites.google.com/uwc.ac.za/permissionresearch/home>

The permission letter must then be submitted to BMREC for record keeping purposes.

The Committee must be informed of any serious adverse event and/or termination of the study.

A handwritten signature in black ink, appearing to read 'Josias'.

*Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape*

NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

Appendix D

Quality Assessment Tool

Major Components	Response options		
1. Was the research question or objective in this paper clearly stated?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
2. Was the study population clearly specified and defined?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
3. Was the participation rate of eligible persons at least 50%?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
4. Were all the subjects selected or recruited from the same or similar populations (including the same time)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
5. Was a sample size justification, power description, or variance and effect estimates provided?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported

10. Was the exposure(s) assessed more than once over time?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
12. Were the outcome assessors blinded to the exposure status of participants?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
13. Was loss to follow-up after baseline 20% or less?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
Quality Rating	Good	Fair	Poor
Additional Comments (If Poor, please state why):			

Source: The National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies