

**ADHERENCE TO THE DAPIVIRINE VAGINAL RING AMONG WOMEN
IN AFRICA: A SYSTEMATIC REVIEW AND META-ANALYSIS**

**ADHERENCE TO THE DAPIVIRINE VAGINAL RING AMONG WOMEN IN AFRICA:
A SYSTEMATIC REVIEW AND META-ANALYSIS**

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for the Degree Master of Science

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List of Abbreviations and Symbols

DVR	Dapivirine Vaginal Ring
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
MWI	Malawi
TZA	Tanzania
ZAF	South Africa
ZWE	Zimbabwe
KEN	Kenya
UGA	Uganda
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
EMA	European Medicines Agency
PrEP	Pre-Exposure Prophylaxis
PRISMA	Preferred Reporting Items for Systematic Reviews
WHO	World Health Organization
ARV	Antiretroviral Drug
UNDP	United Nations Development Program
UNAIDS	Joint United Nations Programme on HIV/AIDS
PEP	Post-exposure prophylaxis
CDC	Centers for Disease Control and Prevention – Global HIV & TB
ARV	Antiretroviral Drug
ART	Antiretroviral Treatment

SDGs	United Nations Sustainable Development Goals
GRADE	Grading of Recommendations Assessment, Development and Evaluation.
PICO	Population, Intervention, Comparator, and Outcome
N	Number of participants included in the study
HiREB	Hamilton Integrated Research Ethics Board

Lay Abstract

Even though there are many ways to protect against HIV, like the Dapivirine Vaginal Ring (DVR) made for women, some people still get infected. Using the ring exactly as the doctor recommends helps lower the chance of getting HIV, even if exposed. Our research focused on how many women aged 16 to 45 in Africa use the ring correctly, the actual number of times women used the ring correctly, and, narratively, by how many visits/rings indicated adherence. We looked at all the available information on the DVR up to December 2024. After registering the study in a research database called PROSPERO (CRD42024593018) and collecting and analyzing the data, we found that about 83% of users used the ring the right way. Factors like age, country, and whether they could feel the ring during sex played a role in how well it was used. These findings suggest that some women in Africa don't use the ring as recommended, which means they may still be at risk of HIV even when they have the ring.

Abstract

Introduction: Despite the availability of HIV preventive measures, new HIV infections are still on the rise. The Dapivirine Vaginal Ring (DVR), a silicone circular ring, continuously distributes Dapivirine into the vagina to prevent HIV infection. The objective of this systematic review is to summarize the evidence on adherence to DVR for HIV-1 prevention among women in Africa and to describe the factors associated with adherence.

Methods and Analysis:

This thesis comprises two separate publishable manuscripts (a published protocol with Health Science Reports and an article currently in press with PLOS Global Public Health). The core parts of this thesis include: chapter one, where a comprehensive summary of evidence on HIV, Pre-Exposure Prophylaxis, Dapivirine Vaginal Ring, adherence, and other components is described. There is limited evidence on the extent of DVR adherence among females in Africa, as well as factors associated with existing adherence. This formed the basis for the study that is conducted in this thesis. In chapter two, details on how the thesis was conducted are presented. That is: a systematic review of studies in which DVR was used to prevent HIV-1 in African women. We searched MEDLINE, Global Health, CINAHL, and EMBASE from database inception to December 2024. We included observational studies and randomized trials of females between 16 and 45 years of age, resident in Africa, who have used the DVR. Our primary outcome was adherence to DVR explored as women adhering, mean adherence, and visit/rings adhering. Pairs of reviewers independently screened for eligible studies and extracted relevant data. We performed a random-effects meta-analysis of proportions and mean for DVR adherence. The certainty of the evidence was assessed using the GRADE approach.

Results and Discussion:

In chapter three, we presented the study findings according to the study-specific objectives.

Chapter four of the thesis discusses a summary of the methodological issues, future directions, and review conclusions will be presented. As such, our search retrieved 217 records, of which 15 published between 2016 and 2024 were found. Across the seven included studies, there were a total of 2,424 DVR women users reported in four studies, 1,552 participants in the two studies reporting mean adherence, 27,904 follow-up visits, and 14,034 rings distributed. Adherence to the DVR among women was generally high, with a pooled estimate of 83%, although the certainty of evidence was very low. Mean adherence scores also suggested good adherence, with a pooled mean of 3.34 (95% CI: 3.00–3.67). There were 74% (95% CI: 74–75%) of rings used well and 89% (95% CI: 89–90%) of visits with adherence. Factors influencing adherence included individual characteristics (e.g., education level, country), partner-related aspects (e.g., partner feeling the ring during sex), ring-related challenges (e.g., difficulty inserting the ring), and environmental influences (e.g., discussing the study with non-study staff).

Conclusion

The evidence suggests generally good adherence to the DVR, which may enhance its effectiveness in reducing HIV infections in real-world settings; however, the certainty of this evidence is low. Given this limitation, we recommend that DVR use be accompanied by additional prevention methods, such as condoms. We also encourage further implementation research, particularly individual patient data meta-analyses, to assess adherence more accurately. These efforts can provide critical insights for developing targeted strategies to improve adherence and generate comprehensive pooled estimates to better inform practice and policy.

Protocol Registration

This study was registered on Prospero (CRD42024593018).

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I would first like to thank my supervisor and mentor, Prof. Lawrence Mbuagbaw, for his continuous support throughout my academics and professional development over the years. I truly appreciate his wisdom as a mentor, providing me with guidance throughout the research process, networking, and scientific communication. I am also glad he has continuously trusted and believed in my capabilities. I am very grateful to Ms. Rachel Couban for agreeing to mentor me on aspects of database search and literature review, a skill that became a reality after working under her mentorship. I would also like to thank my thesis committee members, Drs. Giulia Muraca and Behnam Sadeghirad, for their time and guidance towards the completion of this work. Their knowledge and critical insight aided in the development and refinement of this thesis.

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Table of Contents

List of Abbreviations and Symbols.....	4
Lay Abstract	6
Abstract	7
Acknowledgments.....	10
Declaration of Academic Achievement	14
Chapter 1: Introduction	15
1.1. HIV Epidemic Overview	15
1.2. PrEP Development	16
1.3. Overview of Dapivirine Vaginal Ring (DVR)	17
1.4. Rationale	19
1.5. Chapters Outline	20
1.6. Research Objectives	21
Chapter 2: Study Protocol	23
2.1. Background	23
2.2. Methods	25
2.2.1. Protocol Registration and Standard Reporting	25
2.2.2. Study Selection	25
2.2.3. Information Sources	25
2.2.4. Data Management	26
2.2.5. Study Screening	26
2.2.6. Data Abstraction and Risk of Bias Assessment	26
2.2.7. Statistical Analysis	27
2.2.8. Assessment of Certainty in Evidence	27
2.2.9. Patient and Public Involvement	28
2.2.10. Ethical Approval	28
2.3. Discussion	28
Chapter 3: Systematic Review and Meta-Analysis Results	30
3.1. Background	30
3.2. Methods	32
3.2.1. Review Registration and Standard Reporting	32
3.2.2. Eligibility	33
3.2.3. Information Sources	33
3.2.4. Study Selection	33

3.2.5. Data Abstraction and Conversion	34
3.2.6. Risk of Bias Assessment.....	35
3.2.7. Statistical Analysis	35
3.2.8. Subgroup Analysis	36
3.2.9. Meta-regression Analysis	36
3.2.10. Assessment of Certainty in Evidence	36
3.3. Results	36
3.3.1. Results of Search.....	36
3.3.2. Characteristics of Included Studies.....	38
3.3.3. Characteristics of Included Studies.....	38
3.3.3.1. Dapivirine Vaginal Ring Treatment Characteristics.....	38
3.3.3.2. Characteristics of Primary and Secondary studies included	41
3.3.3.3. Characteristics of Meta-Analysis Included Studies	41
3.3.4. Characteristics of Excluded Studies.....	42
3.3.5. Risk of Bias	42
3.3.6. Proportion of women adhering to Dapivirine Vaginal Ring (DVR)	43
3.3.7. Mean Adherence to Dapivirine vaginal Ring (DVR).....	44
3.3.8. Proportions of Rings Used and Follow-up Visits Reflecting Adherence to the Dapivirine Vaginal Ring (DVR).....	45
3.3.9. Publication Bias	45
3.3.11. Factors Associated with Dapivirine Vaginal Ring (DVR) Adherence	49
3.4. Discussion.....	50
Chapter 4: Summary of Methodological Issues, Future Directions, and Review Conclusions.....	53
4.1. Strengths and Limitations.....	53
4.2. Future Directions Based on Study Findings.....	53
4.3. Conclusion.....	54
References	55
Appendices	
1. Data Search.....	64
2. Characteristics of Excluded Studies	72

List of Tables

Table 1: Characteristics of Included Publications	40
Table 2: Characteristics of Primary and Secondary Publications Captured	41
Table 3: Characteristics of Included Studies in the Meta-Analysis on Dapivirine Vaginal Ring	42
Table 4: Summary of Findings Table for Certainty of Evidence.....	47
Table 5: Factors Associated with DVR Adherence in 15 Publications	50

List of Figures

Figure 1: PRISMA flow diagram for study	37
Figure 2: Risk of Bias Assessment in Included Studies for this Systematic Review	43
Figure 3: Individual studies and pooled estimates of women aged 16 and 45 years in Africa adhering to the Dapivirine Vaginal Ring.	44
Figure 4: Individual studies and Mean Pooled Estimates of Women Aged 16 and 45 Years in Africa Adhering to the Dapivirine Vaginal Ring.....	44
Figure 5: Individual Studies and Pooled Estimates of Adherence to the Dapivirine Vaginal Ring Across Follow-up Visits and Ring Use.	45

Declaration of Academic Achievement

Together with my supervisor, Prof. Lawrence Mbuagbaw, we conceptualized the original idea for this research. The search strategy was developed in collaboration with Ms. Rachel Couban from the Health Sciences Library at McMaster University. I later wrote the first draft of this thesis and created the tables and figures, with subsequent feedback and suggestions from my supervisor and my committee members. Individuals who contributed will be included as co-authors in the published manuscript(s) resulting from this work.

I, Roseline Dzekem Dine, therefore declare that this thesis is my work. To the best of my knowledge, the content of this document does not infringe on anyone's copyright.

Chapter 1: Introduction

In this chapter, we will cover some background information on Human Immunodeficiency Virus (HIV) and Pre-exposure prophylaxis (PrEP). The chapter will also describe the Dapivirine Vaginal Ring (DRV), including existing literature on its efficacy and safety. This will help inform the actual knowledge translation gap related to DRV that needs to be explored, hence the thesis objectives.

1.1. HIV Epidemic Overview

HIV has infected more than 60 million people and led to a decline in CD4 cells and Acquired Immunodeficiency Syndrome (AIDS). (1) To date, close to 40 million have died. (2,3) About 80% of HIV is contracted through mucosal surfaces, mostly through sexual intercourse, percutaneous, and perinatal routes. (4,5)

In 2023, the global prevalence of HIV was estimated at 39.9 million, with about 1.3 million new infections. Of all the new HIV infections, 53% were girls and women, accounting for 44% of all new infections. (6) In sub-Saharan Africa, women and girls accounted for 63% of new HIV infections. (6)

Stakeholders globally, including the Centers for Disease Control and Prevention – Global HIV & TB (CDC), the United Nations Development Program (UNDP), and the World Health Organization (WHO), remain dedicated to helping the global community eliminate HIV. (3) These stakeholders have worked tirelessly to support frameworks and set milestones, including the United Nations Sustainable Development Goals (SDGs) to end HIV by 2030 and the Joint United Nations Programme on HIV/AIDS (UNAIDS) 95-95-95 Targets by 2025. (1) Reports state that although certain nations—including Botswana, Eswatini, Rwanda, Tanzania, and Zimbabwe—

have made great strides in reaching the 95–95–95 targets, the uncontrolled viral load and new cases continue. (1)

Factors linked to the persistent growth of HIV, especially among women of reproductive age, include risk-taking behaviors among youths, inadequate or poor structure of sexual and reproductive health services, separated spouses, long distances between the place of residence and health facility, low income, and poor media exposure. (7–10) Furthermore, gender inequality, discrimination, violence, stigma, and unfavorable laws continue to prevent a considerable number of people and communities, particularly women and important populations, from accessing HIV care and services. (3)

Different management approaches for HIV exist. These include the antiretroviral treatment (ART), which reduces the viral load in already infected individuals. (11) As global attention towards ending HIV continues, stakeholders came to a scientific consensus that patients with an undetectable viral load for at least six months were not able to transmit HIV. (12) Even at this point, HIV prevention tools such as condoms, as well as the fairly new methods of PrEP and post-exposure prophylaxis (PEP), remain useful. (1)

1.2. PrEP Development

PrEP is an HIV prevention treatment taken by people who are at risk of getting infected with HIV. (13) Since its launch in 2012, PrEP has been demonstrated to be more effective when taken exactly as prescribed, lowering the risk of HIV infection by 27% to 99% compared to no PrEP. (13–15) Pharmacological interventions for PrEP can be taken orally, injected, or administered through the vagina. Though PrEP is designed for all groups of people, the primary target population includes

men who have sex with men, transgender individuals, and persons who inject drugs due to their heightened risk of acquiring HIV. (16)

PrEP treatment options include Apretude, a long-acting injection with antiretroviral cabotegravir given once every two months; Truvada, an oral daily method combining tenofovir, disoproxil, and emtricitabine; as well as Descovy, an oral daily method containing tenofovir alafenamide and emtricitabine. (15,17–19) The use of PrEP has not been without barriers and challenges that include poverty, discrimination, and gender inequality. (20)

Therefore, there is a need for a new HIV biomedical prevention tool to curb rates and meet the specific needs of different genders, such as women. (21) This is important, especially in settings where women are at a high risk of sexual violence and in scenarios where they have limited abilities to negotiate for safe sex practices. (22) As a result, new discreet tools such as the DVR have been introduced for women.

1.3. Overview of Dapivirine Vaginal Ring (DVR)

DVR discovery started in 2004, intending to provide women more control over HIV prevention. (21) DVR is also a tool that promotes women's sexual rights by providing a discreet HIV preventive technique for women living in disadvantaged situations and who may experience sexual violence. (22) DVR is a non-nucleoside HIV-1 reverse transcriptase inhibitor that works against a wide range of HIV-1 subtypes. The ring itself is made of flexible silicone, measuring 25mm in diameter and 7.7mm thick. It contains 25mg of the antiretroviral drug (ARV) Dapivirine, dispersed uniformly throughout the material, slowly over 28 days into the vagina, at the site of potential infection. DVR prevents HIV from making copies of

itself inside healthy cells few hours after insertion. The DVR has a shelf life of up to 60 months when stored at or below 30°C. (23,24)

In phase 1 and 2 trials, DVR was found to be tolerable in terms of safety and acceptability. (17,25–28) Data from phase 3 randomized, double-blind, placebo-controlled trials showed that DVR had a relative risk reduction from 27% to 31% for HIV infection. (23,29) Adherence to the ring is often assessed in two or three categories based on the levels of drug delivered (0·9 mg or less [no adherence], more than 0·9 mg to 4·0 mg [moderate adherence], and more than 4·0 mg [good adherence]). (29,30) In some trials, self-reports after ring utilization have also been used to assess adherence. (31) DVR gained approval from the European Medicines Agency (EMA) in 2020 and the World Health Organization (WHO) in 2021, as well as national licenses, particularly in Africa, to be added to the list of essential pharmaceuticals. (24,32,33)

At 12 months, the demand rates for DVR—the ability to utilize the ring when available and under almost real-life conditions—were found to be above 60%, an essential component for adherence. Additionally, 88.5% of the participants accepted the DVR. (12,18) Several studies on the ring have investigated the factors associated with DVR adherence. Findings revealed that factors such as disclosing the use of DVR to a supportive person improved adherence. (36) Other studies reported that women who have healthy sexual discussions with their partners are also more likely to adhere to DVR use. (37,38) While adherence to the ring has been shown to vary from about 48% to 90%, (27,39,40) the literature suggests that adherence may be influenced by age, geographic locations, involvement in sex work and marital status. (23,31,41) Known factors that may impede adherence include the risk of urinary tract infection, vaginal discharge, vulvovaginal pruritus (itching), vulvovaginitis, and pelvic pain. (33) Vaginal

bleeding may cause some women to remove DVR due to hygienic concerns, beliefs that the ring could block menstrual flow, fears that the ring would come out with blood or during tampon removal, and fear of overburdening the vagina. (14,42) On the contrary, one study reported that the majority (60%) did not mind wearing the ring during vaginal bleeding and would not remove it (91%). (42)

Strategies to improve ring uptake include working with and training healthcare providers with available guides and friendly counseling techniques to encourage usage; working with non-governmental organizations and community health workers to ensure that the ring is provided in a culturally sensitive manner while addressing stigma, side effects, and myths about the rings. (23)

Despite the above, there are no pooled estimates of adherence to the DVR, (31) limiting the evidence base to guide decision-making and practice. (43) Therefore, this systematic review and meta-analysis aims to summarize evidence on adherence to DVR for HIV-1 prevention among African women and the associated factors.

1.4. Rationale

Evidence on the DVR exists in the literature mainly as primary studies. These studies include the ASPIRE study (N=2,629) that evaluated the safety and efficacy of DVR for the prevention of HIV-1 infection in healthy, sexually active, HIV-negative women. (23) The HOPE study (N= 1456), which was a continuation of the ASPIRE randomized clinical trial, further evaluated the use and safety of DVR in an open-label setting with high background rates of HIV-1 infection. (44) Another study, the RING study (N= 1959), was conducted to determine whether the DVR could help prevent HIV infection in women and was safe for long-term use. (29) Also, in the DREAM study (N=848), additional data were collected to determine the safety data and establish adherence

to DVR. (31) In the REACH study (N= 247), the safety and acceptability of the DVR and Truvada in young women ages 18-21 were determined. (45) An additional objective of the REACH study was to understand what kind of support young women need to use DVR and oral PrEP, as well as their preferences for each. While in the DELIVER study (N= 750), the investigators evaluated the safety and acceptability of DVR and Truvada® as daily oral PrEP in pregnant women. (46) The B-PROTECTED study (N=200) was implemented to characterize the safety, drug detection, adherence, and acceptability of DVR, inserted every four weeks, and a once-daily Truvada (200mg FTC/300 mg TDF) tablet used by women from sub-Saharan African countries during breastfeeding. (47) Among these studies and more, very few have focused on reviewing different components of DVR use (43) despite the advantages such methodological studies could bring in terms of knowledge translation and DVR development. Among these advantages is the potential for evidence from well-conducted evidence synthesis to offer a thorough understanding of DVR use, revealing what and how it works while utilizing a sizable dataset that might not have been achievable with available resources. (48) Evidence from such methodological studies could further help identify research gaps useful to investigational product development and hence improve chances of meeting population needs. With this and background knowledge of DVR effectiveness solely depending on the level of adherence, it is apparent that methodological studies synthesizing evidence are imminent.

1.5. Chapter Outline

This thesis will be divided into four different chapters. Chapter one is a summary of the HIV pandemic in terms of global trends, most affected groups, treatment, and prevention. This was followed by a deep summary on PrEP while focusing on DVR and adherence. Additionally, the

rationale for why a pooled estimate is needed was captured, including a summary of the thesis structure and objectives. Chapter two of this thesis will present details on how the thesis objectives will be met. To achieve this, we will write a protocol illustrating the plans for identifying, choosing, assessing, and summarizing relevant studies. The inclusion and exclusion criteria that will follow a Population, Intervention, Comparator, and Outcome (PICO) framework will be used. Also, an elaborate search strategy and processes with terminologies including DVR, age, and regions will be developed with the help of a well-experienced Liberian. Additional methodological frameworks, such as Preferred Reporting Items for Systematic Reviews (PRISMA) and Grading of Recommendations Assessment, Development and Evaluation (GRADE), will be used to improve the quality of reporting and conduct of this thesis. The statistical approach that will be employed to derive results will also be highlighted in this chapter. In chapter three, we will present findings from the systematic review, including details on the number of studies eligible and those excluded. We will also show pooled estimates on the DVR, as well as which age groups are most likely to adhere to the DVR. Results will generally be presented in the form of text, tables, and figures. Chapter four of this thesis will include a summary of methodological issues, future directions, and overall review conclusions.

1.6. Research Objectives

- a. To determine the prevalence of DVR adherence among females 16-45 years old in Africa.
- b. To measure the mean DVR adherence among women 16-45 years old in Africa.
- c. To measure the proportion of women adhering to DVR visits and ring across different countries in Africa.

- d. To identify factors associated with DVR adherence among females 16-45 years old in Africa.

Chapter 2: Study Protocol

In this chapter, we present the systematic review and meta-analysis protocol that was published in the Health Science Reports (*Dine RD, Muraca G, Sadeghirad B, Mbuagbaw L. Adherence to the Dapivirine vaginal ring among cisgender women in Africa: protocol for a systematic review and meta-analysis. Health Sci Rep. 2025;8(7): e71057. doi:10.1002/hsr2.71057*). This protocol was developed to provide a step-by-step guide that anyone can use to conduct similar reviews around the world.

2.1. Background

Several evidence exist on HIV prevalence and how it affects diverse groups of people around the world. (6) Prevention measures, including Pre-Exposure Prophylaxis (PrEP), were introduced in 2012 and have been in use ever since. (13–15) PrEP is administered in different formulations (3) and can be used for either long or short-term periods. (15,17–19) Though these PrEP methods exist with high prevention rates, women's and girls' vulnerability is not fully considered (21), especially in settings where women are at high risk of sexual abuse. (22) As a result, new methods such as Dapivirine Vaginal Ring (DVR) are introduced. (21) The ring offers women a less user-dependent option to control HIV infection by releasing the antiretroviral medication Dapivirine once a month with little systemic effects. (23,24) In phase trials on the safety and acceptability of DVR, it was found to be tolerable. (17,25–28) It has also been found to have a relative risk reduction ranging from 27% in the ASPIRE study to 31% in the Ring study. (23,29) Adherence to the ring is often assessed in different categories (29,30), which could also be assessed as simply as self-reports of “YES” or “NO”.(31)

It has been found that factors such as disclosing the use of DVR to a supportive person improved adherence. (36) Additionally, women who had healthy sexual discussions with their partners were also likely to adhere to DVR use (37,38), leading to DVR adherence ranging approximately between 48% to 80% (27,39,40), with some groups of women, such as sex workers, more likely to adhere than others. (41)

Evidence indicates that vaginal bleeding causes some women to remove DVR due to hygienic concerns, beliefs that the ring could block menstrual flow, fears that the ring would come out with blood or during tampon removal, and fear of overburdening the vagina. (14,42) Nevertheless, some studies showed that the majority (60%) of women aged 18-45 years old did not mind wearing the ring during vaginal bleeding and would not remove it (91%). (42)

Despite these challenges and concerns, the European Medicines Agency (EMA) considered them manageable given the presumed benefits and protection DVR provides to women. (33) Strategies to improve ring uptake include working with and training healthcare providers with available guides and friendly counseling techniques to encourage usage; working with Non-Governmental organizations and community health workers to ensure that the tool is provided in a culturally sensitive manner while addressing stigma, side effects, and myths about the rings. (23)

The background highlighted a need to pool evidence on DVR to provide a broader understanding of adherence using a wide range of data covering different age groups and settings. These findings might be relevant for outreach prioritization consideration and tool development. Therefore, the objective of this systematic review and meta-analysis is to summarize the evidence on adherence to DVR for HIV-1 prevention and to aggregate findings.

2.2. Methods

2.2.1. Protocol Registration and Standard Reporting

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols checklist was followed to report our study protocol. (49) This protocol is registered with PROSPERO (registration number CRD42024593018). Findings from this study were reported in accordance with the PRISMA guidelines. (50)

2.2.2. Study Selection

We will include clinical trials of any phase and design (e.g. cross-over and cluster trials) and observational studies (e.g. cohort studies) that (1) enrolled sexually active women (16 and 45 years old), (2) measured DVR with or without another active drug for 7 days or more, and (3) reported adherence to DVR for at least 28 days. We will exclude studies that (1) will not be completed at the time of data extraction or do not include a measure of adherence, and (2) review-type articles, editorials, case reports, and letters to the editor. In research involving varied patient groups and products or men, we will only include data from eligible populations if the findings are reported separately.

2.2.3. Information Sources

We will search MEDLINE, Global Health, and EMBASE via OVID platforms and CINAHL via the EBSCO platform from database inception to December 2024 without any language restriction. We will also conduct a review of gray literature using Google search and the reference list of all

included articles to identify any study that meets our inclusion criteria. An experienced Liberian will develop database-specific search strategies. A draft of our search strategy is shown (Appendix 1) with Africa filters borrowed from Pienaar E. et al, 2021. (51) We will contact content experts and opinion leaders in this clinical area to identify potentially eligible trials.

2.2.4. Data Management

We will download the identified citations in each database and export them into the EndNote 21 reference manager to combine and deduplicate.

2.2.5. Study Screening

Pairs of reviewers will independently screen titles, abstracts, and full-text articles retrieved from the searchers using COVIDENCE.

2.2.6. Data Abstraction and Risk of Bias Assessment

Using standardized, pilot-tested forms, trained reviewers, will independently and in duplicate, extract the following information from eligible studies: (i) study characteristics [author's name, publication year, study design (observational, quasi-randomized, and randomized), country of origin, and funding source], (ii) population-related information [age and age grouping, level of education, marital status, income, partner knowledge of ring use, transactional sex, number of episodes of vaginal sex, and use of contraceptive methods such as condom], (iii) duration of treatment, and (iv) adherence. Adherence to DVR can be measured as self-report, levels of residual drug in the ring, plasma dapivirine concentration, or using electronic approaches (smart rings embedded with sensors). Ultimately, adherence is summarized as the proportion of women with

optimal adherence. Data will be collected from all intervention or control arms, provided that DVR is used. Risk of bias assessments will be conducted both in duplicate and independently. For this study, the risk of bias will be assessed based on the prevalence of adherence, and therefore, the 10-item tool developed by Hoy et al will be adapted. (52) A judgment of high or low can be assigned to each domain, and an overall judgment of high, low, or moderate will be made based on the reviewers' assessment of all 10 items. All disagreements will be resolved through discussion or the involvement of a third reviewer if needed.

2.2.7. Statistical Analysis

Our primary outcome, adherence, will be standardized into one format: those who adhered and those who did not adhere to permit comparison across studies. Continuous results will be presented as mean (SD) or median (IQR) and number (percent) for categorically reported adherence. Continuous data will be pooled as a weighted mean with 95% confidence intervals. For meta-analysis of the adherence rates reported as n (%), we will use the Freeman-Tukey double arcsine transformation to stabilize the variances. (53) All analyses will be conducted using random effect models. Heterogeneity will be determined by visually inspecting forest plots and I^2 –values. Funnel plots will be used to inspect publication bias. (54) The results of the studies will be narratively described when the number of eligible studies is insufficient for meta-analysis or when studies are conceptually heterogeneous and do not warrant pooling. We will use STATA (StataCorp, Release 18 BE, College Station, TX, USA) for all statistical analyses

2.2.8. Assessment of Certainty in Evidence

We will assess the certainty in our pooled estimates using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. GRADE evaluates the following five domains: risk of bias, inconsistency, imprecision of pooled estimates, indirectness, and evidence of publication bias. Based on these domains, the certainty of evidence can be graded as very low, low, moderate, or high. (55)

2.2.9. Patient and Public Involvement

Patients or the general public will not be directly engaged in designing or disseminating the study's results.

2.2.10. Ethical Approval

This study does not require ethical approval because it will rely on primary published data.

2.3. Discussion

Adherence to DVR remains understudied in Africa. (31) This systematic review and meta-analysis will contribute to a better understanding of how DVR adherence aids in preventing HIV-1 infection in women, as well as the factors that influence observed adherence. Its findings can provide important foundational knowledge for future research and innovation in DVR and other PrEP tools. This is especially relevant because some studies have shown that certain groups of women adhere better than others. (23,31,41) Such knowledge might introduce implementation research in other parts of Africa for women with similar risk towards HIV prevention. Additionally, findings might help scale up uptake, especially among women in humanitarian settings where violence rates might increase. Furthermore, understanding the trends of adherence would help us tailor

suggestions on strategies to meet the identified specific needs of women and girls, including community outreach towards ring use and adherence. Our findings may also encourage policymakers in Africa to include the DVR in their essential drug packages, particularly in Southern and Eastern Africa, where HIV prevalence is increasing. (6)

This review will first be submitted to McMaster University as part of a master's degree program requirement. They will also be published in a peer-reviewed journal and discussed at a conference targeting policymakers.

Chapter 3: Systematic Review and Meta-Analysis Results

This chapter specifically focuses on the findings from the systematic review and meta-analysis results as described in depth in Chapter Two. The results provide high-level evidence to support existing knowledge and findings on the Dapivirine Vaginal Ring (DVR) adherence among women in Africa. These findings are currently under publication consideration in PLOS Global Public Health. Additionally, the abstract was accepted for a poster presentation at the International Conference on AIDS and Sexually Transmitted Diseases in Africa (ICASA), Ghana.

3.1. Background

In 2023, the global prevalence of HIV was estimated at 39.9 million, with approximately 1.3 million new infections. Girls and women represented 53% of prevalent cases and 44% of all new infections. (6) Pre-Exposure Prophylaxis (PrEP), an HIV prevention treatment taken by people at risk of HIV infection, has been in use as a strategy to curtail HIV transmission. (13) Since its launch in 2012, PrEP has been demonstrated to be more effective, with studies showing an estimated reduction in HIV infection between 27% and 99% when compared with no PrEP. (13–15) Pharmacological interventions for PrEP can be taken orally or by injection. These included Apretude, a long-acting injection with antiretroviral cabotegravir given once every two months; Truvada, an oral daily method combining tenofovir, disoproxil, and emtricitabine; as well as Descovy, an oral daily method containing tenofovir alafenamide and emtricitabine. (15,17–19)

Multiple PrEP methods exist with a high prevention rate against HIV infections when used as intended; however, new HIV preventative methods are still required to meet the specific needs of girls and women. (21) This is important, especially in settings where girls and women are at a

high risk of sexual violence and in scenarios where they have limited abilities to negotiate for safe sex practices. (22) Dapivirine Vaginal Ring (DVR) was developed to provide girls and women aged 16-45 years more control over HIV prevention. (21) DVR is an approach that promotes women's sexual rights by providing a discrete HIV preventive technique for women living in disadvantaged situations who may experience sexual violence. (22)

DVR is a non-nucleoside HIV-1 reverse transcriptase inhibitor that works against a wide range of HIV-1 subtypes. DVR provides women with a less user-dependent option by releasing the antiretroviral medication, Dapivirine, once a month, 24 hours after insertion, with little systemic effects. (23,24) Studies on DVR started in 2004. In phase 1 and 2 trials, the safety and acceptability of Dapivirine were tolerable. (17,25–28) Data from phase 3 randomized, double-blind, placebo-controlled trials showed that DVR had a relative risk reduction of HIV infection from 27% to 31%. (23,29) Adherence to the ring is often assessed based on the levels of drug delivered (0.9 mg or less [no adherence], more than 0.9 mg to 4.0 mg [moderate adherence], and more than 4.0 mg [good adherence]). (29,30) In some trials, self-reports after ring utilization have also been used to assess adherence. (31) DVR gained approval from the European Medicines Agency (EMA) in 2020 and, World Health Organization (WHO) in 2021, as well as national licenses, particularly in Africa, to be added to the list of essential pharmaceuticals. (24,32,33)

At 12 months, the demand rates for DVR—the ability to utilize the ring when available and under almost real-life conditions—were found to be above 60%, an essential component for adherence. Additionally, 88.5% of the participants accepted the DVR. (12,18) Several studies have investigated the factors associated with DVR adherence. Findings revealed that factors such as disclosing the use of DVR to a supportive person improved adherence. (36) Other studies reported

that women who have healthy sexual discussions with their partners are also more likely to adhere to DVR use. (37,38) While adherence to the ring has been shown to vary from about 48% to 90%, (27,39,40) adherence is modified by age, geographic locations, involvement in sex work and marital status. (23,31,41) Although early studies anticipated low adherence due to limited awareness of the DVR and concerns about side effects, adherence may also be hindered by known factors such as urinary tract infections, vaginal discharge, vulvovaginal pruritus, vulvovaginitis, and pelvic pain. (33) Vaginal bleeding may cause some women to remove DVR due to hygienic concerns, beliefs that the ring could block menstrual flow, fears that the ring would come out with blood or during tampon removal, and fear of overburdening the vagina. (14,42) On the contrary, one study reported that the majority (60%) did not mind wearing the ring during vaginal bleeding and would not remove it (91%). (42)

Strategies to improve ring uptake have been noted to include working with and training healthcare providers with available guides and friendly counseling techniques to encourage usage; working with non-governmental organizations and community health workers to ensure that the ring is provided in a culturally sensitive manner while addressing stigma, side effects, and myths about the rings. (23) There are no pooled estimates of adherence to the DVR,(31) limiting the evidence base to guide decision-making and practice. (43) The objective of this systematic review was to summarize the evidence on adherence to DVR for HIV-1 prevention and the associated factors.

3.2. Methods

3.2.1. Review Registration and Standard Reporting

This review was registered with PROSPERO (registration number CRD42024593018). Findings from this study are reported according to the PRISMA guidelines. (50)

3.2.2. Eligibility

We included randomized and quasi-randomized trials, prospective or retrospective cohort studies, case-control studies, longitudinal (one-arm) observational studies (time-series and before-after studies), and case series with more than 10 female participants with data on DVR adherence from Africa aged 16-45 years old. We excluded qualitative studies or studies without final results.

3.2.3. Information Sources

An experienced medical librarian (R.C.) developed search strategies specific to individual databases for the review questions. We searched MEDLINE, Global Health, and EMBASE via OVID platforms and CINAHL via the EBSCO platform from database inception to December 2024 without any language restriction. We also conducted a review of gray literature using Google search as well as the reference lists of all included for possible articles or records of information around DVR. Our search strategy included terms for Dapivirine Vaginal Ring, DVR, and adherence (Appendix 1: see Data search (see Supporting Information)).

3.2.4. Study Selection

Pairs of experienced reviewers screened titles and abstracts of identified citations independently, using a standardized, pilot-tested form. Subsequently, reviewers assessed the eligibility of full texts of potentially eligible studies. Reviewers resolved disagreements by discussion or adjudication

with a third reviewer (L.M.). We used Covidence online systematic review software to screen titles and abstracts, full-text articles, and to abstract data. (56)

3.2.5. Data Abstraction and Conversion

Using standardized, pilot-tested forms, pairs of reviewers independently extracted the following data from eligible studies:

(i) study characteristics [author's name, publication year, study design (observational, quasi-randomized, or randomized), country of origin, and funding source]; (ii) population-related information/factors associated with DVR adherence [median age and age grouping, level of education, marital status, income, partner's knowledge of ring use, transactional sex, number of episodes of vaginal sex, and use of contraceptive methods such as condoms]; (iii) duration of DVR treatment (all data were converted to months); and (iv) adherence as defined by study authors. In instances where one study had more than one publication, the publication with adherence data was considered for analysis.

Adherence to the ring was typically assessed in two or three categories based on drug release levels: ≤ 0.9 mg (no adherence), >0.9 mg to 4.0 mg (moderate adherence), and >4.0 mg (good adherence). For randomized controlled trials, only data from the treatment arm were extracted. (29,30) When adherence was reported in three categories, the highest level was extracted.

In addition, we extracted the total number of follow-up visits and the number of visits where adherence to the DVR was reported. We also recorded the total number of rings distributed and the number of rings that were returned with evidence of good adherence. We also extracted mean and median adherence values, along with their measures of spread (e.g., standard deviations), to

estimate mean adherence. Where medians were reported, we converted to means and standard deviations used to estimate standard errors. The 25 mg DVR are designed to release about 4 mg over one month under consistent use. Means closer to 4mg indicate better adherence.

As needed, the number of women who were adherent was computed from the percentage adherence rate. Adherence was then standardized into two categories, i.e., Good adherence vs poor adherence to allow comparisons across studies.

3.2.6. Risk of Bias Assessment

The same pairs of reviewers assessed the risk of bias independently. We assessed risk of bias for prevalence of adherence by using the 10-item tool developed by Hoy et al. (52) A judgment of high or low can be assigned to each domain, and an overall judgment of high, low, or moderate was made based on the reviewers' assessment of all 10 items. All disagreements were resolved through discussion or the involvement of a third reviewer if needed (L.M.). The results of these assessments were plotted as bar charts.

3.2.7. Statistical Analysis

We pooled adherence reported in two or more studies using the DerSimonian–Laird random effects model for proportions and means. (57) For proportions, to stabilize variance, we applied the Freeman–Tukey double arcsine transformation. (53) Heterogeneity was determined by visual inspection of forest plots and I^2 values. Pool I^2 estimates were interpreted based on Cochrane categories: 0% to 40%: Might not be important; 30% to 60%: May represent moderate heterogeneity; 50% to 90%: May represent substantial heterogeneity; and 75% to 100%:

Considerable heterogeneity. (58) These ranges were equally used for making conclusions on the effects of adherence. (54) Study results were described narratively when the number of eligible studies was insufficient for meta-analysis or when substantial conceptual heterogeneity precluded data pooling. Results are presented in forest plots as percentages and 95% confidence intervals or mean and standard deviation. We used Stata (StataCorp, Release 18 BE, College Station, TX, USA) for all statistical analyses.

3.2.8. Subgroup Analysis

There was insufficient data to conduct the planned subgroup analysis.

3.2.9. Meta-regression Analysis

A meta-regression to investigate whether the median age of the participants and the year of study completion was not conducted due to limited observations.

3.2.10. Assessment of Certainty in Evidence

We assessed the certainty in our pooled estimates by using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Based on the GRADE five domains of risk of bias, Inconsistency, Indirectness, Imprecision, and Publication Bias, the certainty of evidence was graded as Very Low, Low, Moderate, or High. (55) This was achieved through GRADE Pro. (59)

3.3. Results

3.3.1. Results of Search

Our search retrieved 217 articles (Appendix 1). After removing duplicates, 112 articles remained, which were then screened based on their titles and abstracts, resulting in 45 articles for full-text

screening. Of the 15 publications, four were included in the meta-analysis of proportion of women adhering, two in meta-analysis of mean, and two for narrative synthesis. (Figure 1)

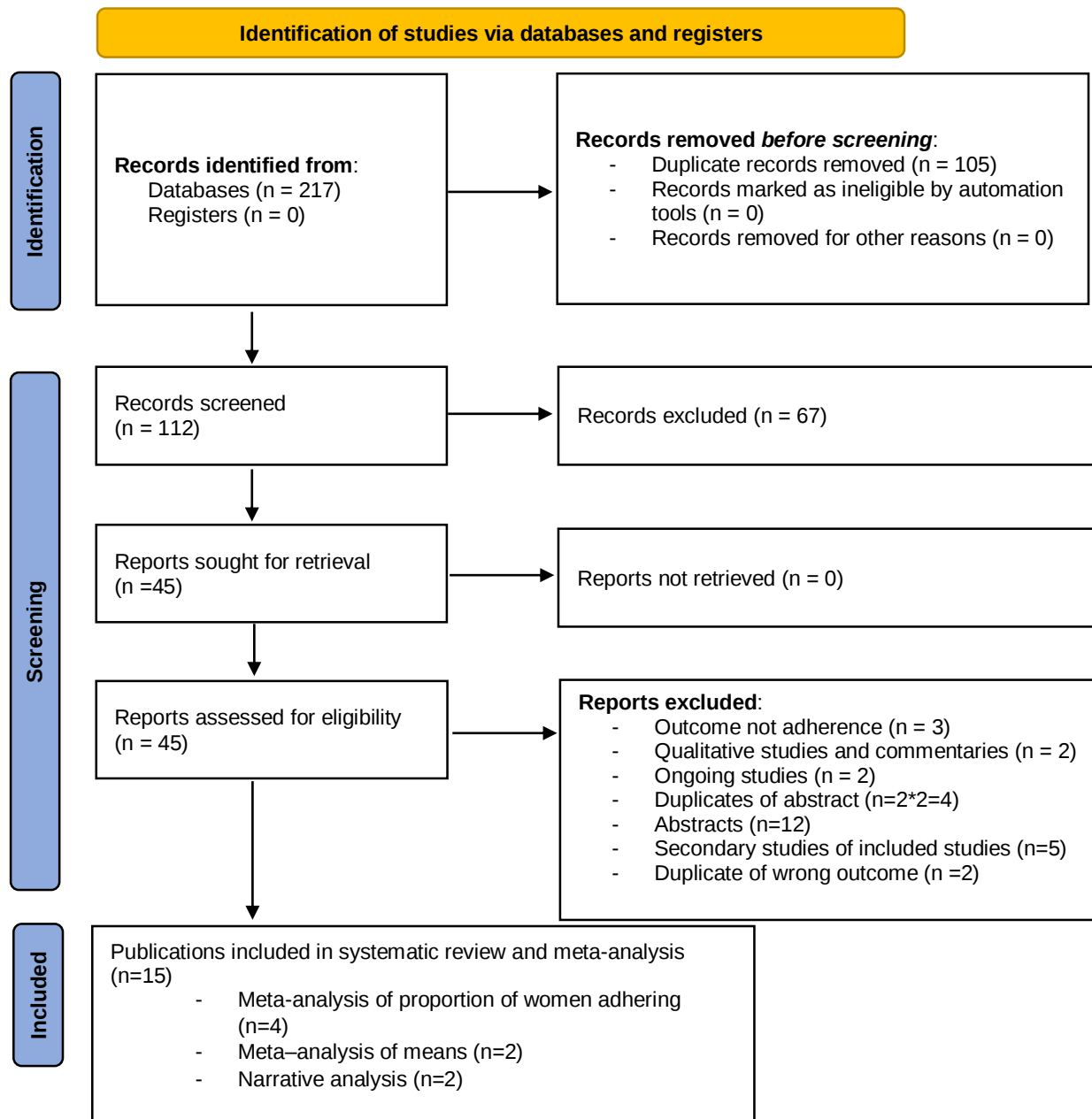


Figure 1: PRISMA flow diagram for study

3.3.2. Characteristics of Included Studies

We found 15 publications, (14,23,28,29,31,35,36,45,60–66) of seven unique studies all conducted among women aged 16-45 years across six African countries (Malawi, Tanzania, South Africa, Zimbabwe, Kenya, and Uganda) (Table 1). Across the seven included studies, there were a total of 2,424 DVR women users reported in four studies, 1,552 participants in the two studies reporting mean adherence, 27,904 follow-up visits, and 14,034 rings distributed.

Only eight studies reported on the factors associated with adherence.

3.3.3. Characteristics of Included Studies

3.3.3.1. Dapivirine Vaginal Ring Treatment Characteristics

DVR was studied in open-label and phase control trials (I-IV) as a single HIV prevention tool (11 studies) or compared with a placebo ring without Dapivirine (two studies). In two studies, it was compared with other PrEP methods such as Truvada (Table 1). In all studies adherence was assessed using residual dapivirine levels in returned rings and only one made use of self-report measure. (28)

Table 1: Characteristics of Included Publications

Study ID	Acronym	Treatment / Control	Country	Sample size	Funding source	Age groups	Year the study was concluded	Design used for data collection
Palanee-Phillips 2018(60)	ASPIRE	Dapivirine Vaginal Ring	MWI, UGA, ZWE, and ZAF	2629	Government	18-45	2015	Observational
Ngure 2024(61)	REACH	Dapivirine Vaginal Ring and Oral FTC/TDF	UGA, ZWE, and ZAF	247	Government	16-21	2021	Randomized Controlled Trial
Roberts 2020(62)	ASPIRE	Dapivirine Vaginal Ring	MWI, UGA, ZWE, and UGA	2629	Government	18-45	2015	Observational
Stoner 2021(36)	HOPE	Dapivirine Vaginal Ring	MWI, UGA, ZWE, and UGA	1432	Government	18-45	2018	Observational
Mayo 2021(63)	ASPIRE	Dapivirine Vaginal Ring	MWI, UGA, ZWE, and UGA	2629	Government	18-45	2015	Observational
Baeten 2021(14)	HOPE	Dapivirine Vaginal Ring	MWI, UGA, ZWE, and UGA	1456	Government	18-45	2018	Randomized Controlled Trial
Nel 2016a(29)	RING	Dapivirine Vaginal Ring	UGA and ZAF	1959	Private	18-45	2015	Randomized Controlled Trial
Baeten 2016(23)	ASPIRE	Dapivirine Vaginal Ring	MWI, UGA, ZWE, and UGA	2629	Government	18-45	2015	Randomized Controlled Trial
Nel 2021(31)	DREAM	Dapivirine	UGA and ZAF	941	Government	18-45	2019	Randomized Controlled Trial
Nair 2023(45)	REACH	Dapivirine ring or daily oral PrEP	UGA, ZWE, and UGA	247	Government	16-21	2021	Randomized Controlled Trial
Nel 2016b(28)	No acronym	Dapivirine and a Placebo Ring	MWI, TZA, KEN, and UGA	280	Private	18-40	2011	Randomized Controlled Trial
Montgomery 2022(64)	CHARISMA	Dapivirine Vaginal Ring	ZAF	96	Government	18-45	2017	Observational
Husnik 2024(65)	ASPIRE	Dapivirine Vaginal Ring	MWI, UGA, ZWE, and UGA	2629	Government	18-45	2015	Observational
Garcia 2021(66)	ASPIRE	Dapivirine Vaginal Ring	MWI, UGA, ZWE, and UGA	2629	Government	18-45	2015	Observational
Browne 2022(35)	ASPIRE	Dapivirine Vaginal Ring	ZAF	713	Government	18-45	2015	Observational

MWI: Malawi, TZA: Tanzania, ZAF: South Africa, ZWE: Zimbabwe, KEN: Kenya, UGA: Uganda

3.3.3.2. Characteristics of Primary and Secondary Studies Captured

Among the 15 publications, there were seven primary studies (14,23,28,29,31,45,64) (Table 2).

Table 2: References of Primary and Secondary Studies on Dapivirine Vaginal Ring

Acronym	Primary Publications	Secondary Publications
ASPIRE	Baeten 2016(23)	Palanee-Phillips 2018(60), Roberts 2020(62), Mayo 2021(63), Husnik 2024(65), Garcia 2021(66), and Browne 2022(35)
DREAM	Nel 2021(31)	No secondary publication on adherence was identified
REACH	Nair 2023(45)	Ngure 2024(61)
No acronym	Nel 2016b(28)	No secondary publication on adherence was identified
HOPE	Baeten 2021(14)	Stoner 2021(36)
RING	Nel 2016a(29)	No secondary publication on adherence was identified
CHARISMA	Montgomery 2022(64)	No secondary publication on adherence was identified

3.3.3.3. Characteristics of studies included in Meta-Analysis

Overall, we identified seven studies that met the criteria for our three main adherence analyses on the Dapivirine Vaginal Ring (DVR). Of these, one study (14) reported both mean adherence and the other number of rings returned with residual drug levels consistent with use (Table 3).

Table 3: Characteristics of Included Studies in the Meta-Analysis

Primary author & year of publication	Studies acronym name	Study Design	Countries	Sample size	N (m)	Mean (SD)	SE	Total follow-up visits (Adherent visits)	Total rings distributed (Adherent rings)
Baeten 2016(23)	ASPIRE	RCT	MWI, UGA, ZWE, and UGA	2629	1313 (1091)	NA	NA	NA	NA
Nel 2021(31)	DREAM	RCT	UGA and ZAF	941	848 (704)	NA	NA	NA	NA
Nair 2023(45)	REACH	RCT	UGA, ZWE, and UGA	247	123 (70)	NA	NA	NA	NA
Nel 2016b(28)	No acronym	RCT	MWI, TZA, KEN, and UGA	280	140 (101)	NA	NA	NA	NA
Baeten 2021(14)	HOPE	RCT	MWI, UGA, ZWE, and UGA	1456	NA	3.2 (1.33)	0.04	NA	14,034(12,530)
Montgomery 2022(64)	CHARISMA	Observational	ZAF	96	NA	3.55(1.66)	0.17	NA	NA
Roberts 2020(62)	ASPIRE	Observational	MWI, UGA, ZWE, and UGA	2629	NA	NA	NA	27,904 (20,699)	NA

MWI:** Malawi, **TZA:** Tanzania, **ZAF:** South Africa, **ZWE:** Zimbabwe, **KEN:** Kenya, **UGA:

***Uganda; N:** Number of people in whom adherence was measured; **m:** Number of people with good adherence, **NA:** Not Applicable, **SD:** Standard Deviation, **SE:** Standard Error*

3.3.4. Characteristics of Excluded Studies

Among the 30 studies that were excluded from this analysis, three did not report the outcome of interest, three were qualitative and commentary studies, four were duplicates of abstracts, five were secondary studies of included studies, and two had wrong outcomes. Further, 12 were abstracts. Two studies were ongoing. (46,47) A list of excluded studies is reported (appendix 2).

3.3.5. Risk of Bias

The overall risk of bias for most of the studies included was judged to be low. The domains with the most concerns were the non-response bias minimization and the representation of the target population. None of the seven studies included used random selection. Also, four did not minimize the likelihood of non-response bias, including the CHARISMA study that only invited a subgroup of participants to respond to their survey questions. Furthermore, none of the studies used a true

sampling frame, and therefore, none met the risk of bias criterion related to sample representativeness. Details of the risk of bias assessments are summarized in Figure 2.

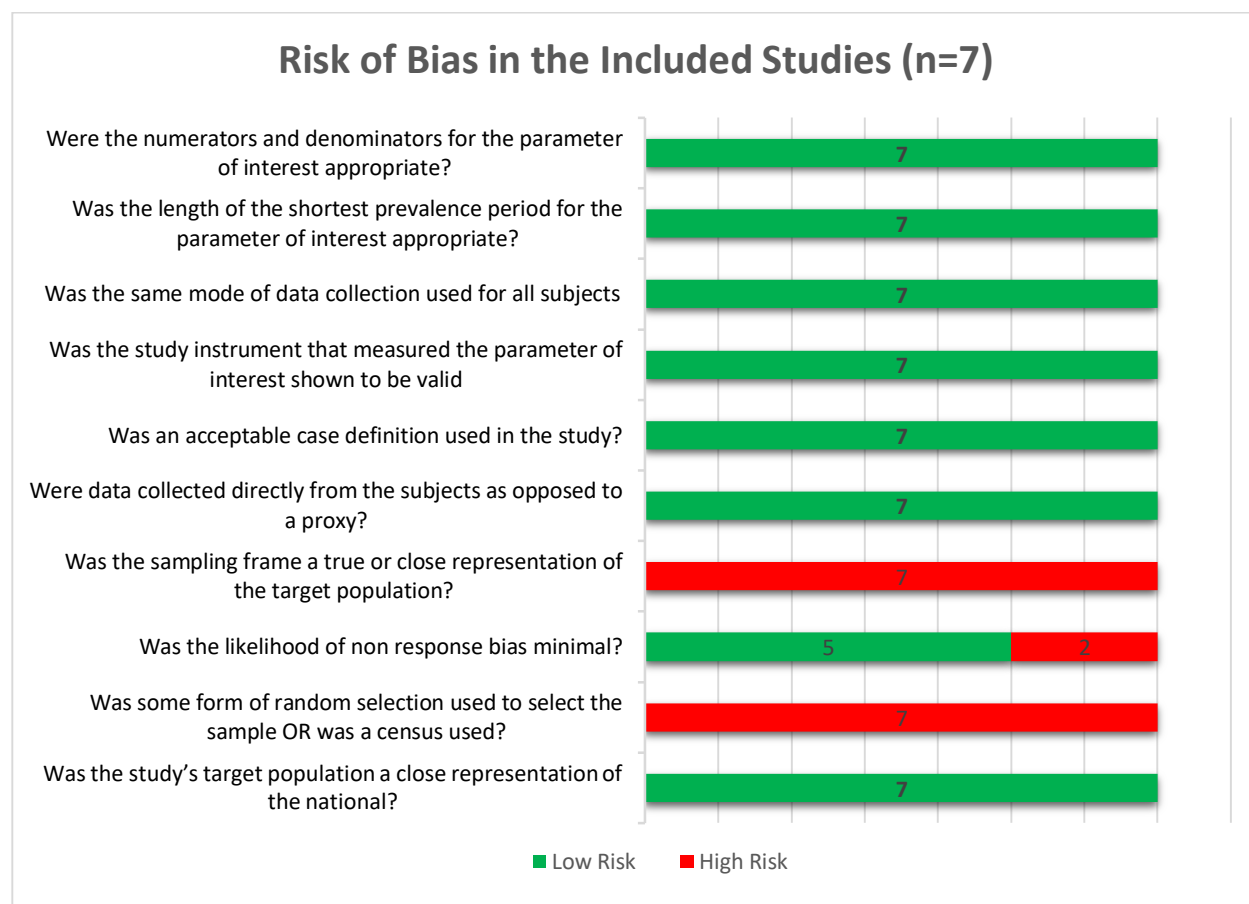


Figure 2: Risk of Bias Assessment

3.3.6. Proportion of women adhering to Dapivirine Vaginal Ring (DVR)

Our meta-analysis from four primary studies reveals the pooled adherence to DVR was 83% (95% CI 59-98%); 4 studies, 2,121 adherent participants; low certainty of evidence. Heterogeneity was considerable ($I^2 = 99.28\%$; Figure 3).

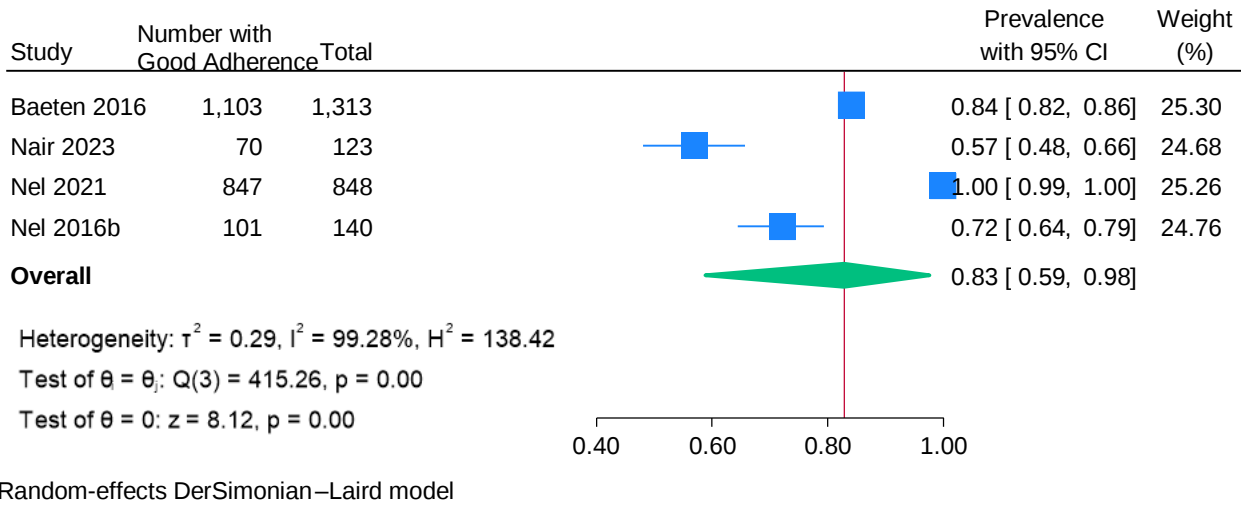


Figure 3: Forest plot of adherence rates to the Dapivirine Vaginal Ring.

3.3.7. Mean Adherence to Dapivirine Vaginal Ring (DVR)

The pooled mean adherence to DVR was 3.34 (95% CI 3.00-3.67); two studies, low certainty of evidence. Heterogeneity was considerable ($I^2 = 75.10\%$; Figure 4).

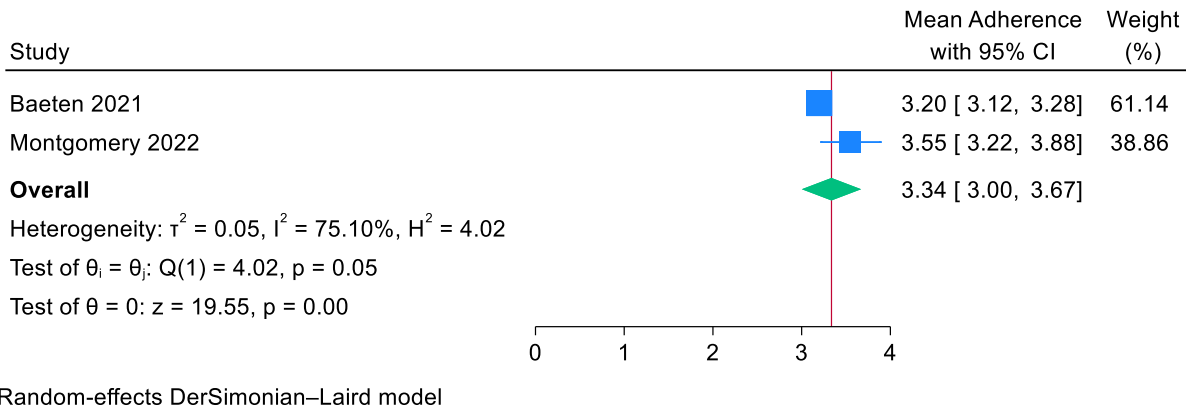


Figure 4: Individual studies and Mean Pooled Estimates of Women Aged 16 and 45 Years in Africa Adhering to the Dapivirine Vaginal Ring.

3.3.8. Proportions of Rings Used and Follow-up Visits Reflecting Adherence to the Dapivirine Vaginal Ring (DVR)

Overall, 74% (95% CI 74-75%) of visits and 89% (95% CI 89-90%) of rings reflected adherence to the DVR with low certainty of evidence (Figure 5).

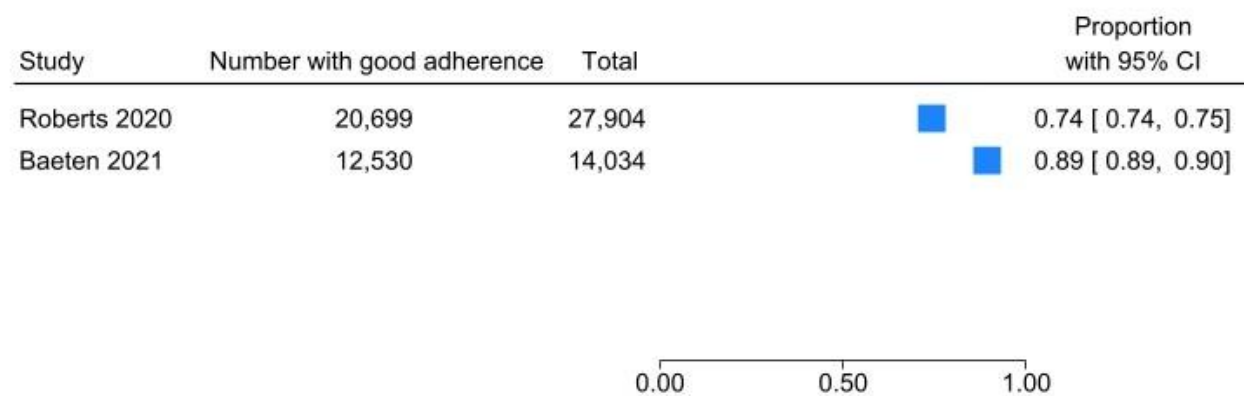


Figure 5: Forest plot of Adherence to the Dapivirine Vaginal Ring for Follow-up Visits and Ring Use.

3.3.9. Publication Bias

We did not conduct Egger’s test for publication bias, as fewer than 10 studies were included in our meta-analysis.

3.3.10. GRADE Findings

Using the GRADE approach, the certainty of evidence was assessed across seven studies included in the meta-analysis. Our findings demonstrated very low certainty of evidence, suggesting limited confidence in the estimated effect This was downgraded by one level due to risk of bias and imprecision owing to high risk of bias in the sampling frame closeness to the target population, random selection, and a deficiency in sample size. We also downgraded the certainty of evidence by two levels for inconsistency, due to a high degree of heterogeneity across the forest plots, with I² values ranging from 75% to 99%. Additionally, we downgraded for indirectness due to

differences between the adherence measures used in the included studies (e.g., adherence categorization) (Table 5).

Table 4: Summary of Findings Table for Certainty of Evidence

Outcomes	Effect size (95% CI)	Relative effect (95% CI)	No of participants/visits/rings (studies)	Certainty of the evidence (GRADE)	Comment
Self-reported adherence	83% (95% CI 59-98%)	-	2424 (4)	⊕○○○ Very low ^{a, b, c, d}	-
Mean adherence	3.34 (95% CI 3.00-3.67)	-	1552 (2)	⊕○○○ Very low ^{e, f, g, h}	-
Visits	74% (95% CI 74-75%)	-	27904 (1)	⊕○○○ Very low ^{i, j}	-
Returned rings	89% (95% CI 89-90 %)	-	14034 (1)	⊕○○○ Very low ^{k, l}	-

CI: confidence interval

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. All pooled studies show low risk of bias in at least one of the domain group. However, the pooled studies show a high risk of bias in the sampling frame closeness to the target population and also in random allocation of participants

b. The studies pooled showed a high rate of heterogeneity with each forest plot results of heterogeneity ranging of 99% which shows the skewness of the effect size of individual studies to

the left and right, thereby resulting in very high variability of results between studies included in the meta-analysis

c. Studies reported levels of adherence in different groups, while some used two groups (good/poor) and others used three groups (poor/moderate/good). To ensure generalization, we used only the good and poor levels of adherence for our study. This process has a possibility of causing a mismatch, leading to indirectness in the evidence synthesized in the meta-analysis

d. Among the four studies included in the first forest plot, two studies had a small sample size of less than 150.

e. Both studies show low risk of bias in at least one of the domain groups. However, the two studies show a high risk of bias in the sampling frame's closeness to the target population and also in the random allocation process

f. The two studies show substantial heterogeneity in the forest plot of mean adherence outcome, which shows the skewness of the effect size of individual studies to the left and right, thereby resulting in slight variability of results between studies included in the meta-analysis

g. Studies reported levels of adherence in percentages, mentioning good adherence without providing more details to better quantify adherence.

h. The two studies might lack precision owing to a deficiency in sample size, thereby affecting the precision of the study.

i. The study shows low risk of bias in at least one of the domain groups. Although a high risk of bias was seen in the sampling frame closeness to the target population and also in the random allocation process

j. Only one study was eligible for this outcome. Therefore, the absence of a pooled estimate and a small sample size downgraded imprecision by two levels

k. The study shows a low risk of bias in at least one of the domain groups. Although a high risk of bias was seen in the sampling frame closeness to the target population and also in the random allocation process

l. Only one study was eligible for this outcome. Therefore, the absence of a pooled effect and a small sample size downgraded imprecision by two levels

3.3.11. Factors Associated with Dapivirine Vaginal Ring (DVR) Adherence

A total of 8 published studies reported factors associated with DVR adherence. These factors are organized as user, partner, ring, and environmental characteristics, together with those that serve as facilitators or barriers to DVR use. In the study, we found factors such as the age group of participants, their education, and income to favor DVR at the user characteristic level, as compared to having an unstable home disfavors the use of the DVR. Factors such as disclosure to a partner of ring use also facilitated the use of DVR as opposed to when the partner felt the ring during sex. Factors such as feeling a ring during sexual intercourse and difficulty in inserting served as barriers to DVR adherence at the product level. Shared social opinion and supportive social opinion about the ring were found to be some of the factors at the environment level that favour DVR adherence (Table 6). (23)

Table 5: Factors Associated with DVR Adherence in 15 Publications

User characteristics	Partner characteristics	Ring characteristics	Environmental characteristics
Facilitators - Age /age group (23,35,61) - Education (61) - Country (66) - Income (61) - Vaginal sex, three months before enrolment(45) - Transactional sex (61) - Use of contraceptive methods(23,61) - Participant engagement activities (66) Barriers - Unstable house (61)	Facilitators - Partners' (primary) knowledge of ring use / had visited the clinic(62) - Disclosure of product use (61) Barriers - Partner felt ring during sex(63)	Facilitators - None Barriers - Felt ring during sex (63) - Very/somewhat difficult to insert (63) - Sometimes/usually uncomfortable to have ring inside every day(63) - One or more grade two or higher adverse events related to DVR during crossover periods(45) - Influence of other PrEP methods (45) - Some/most of the time aware of the ring during normal activities(63)	Facilitators - Social contributors with highly influential views(36) - Supportive social opinions about the ring(36) - Social opinions shared by participants(36)

3.4. Discussion

Overall, despite very low certainty of evidence, adherence to the DVR among women appeared to be high, with a pooled estimate of 83% (95% CI: 59–98%), though individual study estimates varied from 50% to 80%. Mean adherence scores also suggested good adherence, with a pooled mean of 3.34 (95% CI: 3.00–3.67) and study-level means ranging from 3.20 to 3.55. Similarly, adherence based on the number of rings used and visits attended was high, estimated at 74% (95% CI 74-75%) and 89% (95% CI 89-90 %), respectively. Adherence to the DVR was influenced by multiple factors, including individual characteristics (e.g., education level and country), partner-

related factors (e.g., whether the partner felt the ring during sex), ring-related factors (e.g., difficulty inserting the ring), and environmental factors (e.g., discussing the study with non-study staff)

The high adherence observed in this study might be explained by the diverse strategies used to engage community members, which is observed in the number of follow-ups. Further, women included in the studies might have had a better understanding of the ring and are keen on health matters, even though findings demonstrate high heterogeneity. The heterogeneity in DVR adherence observed across included studies may be explained by differences in study populations, settings, and methodologies. Similarly, in the factors associated, we identified that the age group of women was associated with adherence to DVR. (23,35,61) Specifically, younger women under the age of 26 are known to have lower adherence rates than their older counterparts. (23) This may mean they need support to adhere to and improve treatment outcomes. Low adherence in this age group has not been reported only in the use of DVR but also in research focusing on sexual health interventions, where young people may fail to adhere to alternative PrEP techniques. (67,68) Factors associated with low adherence to DVR include the risk of urinary tract infection, vaginal discharge, vulvovaginal pruritus (itching), vulvovaginitis, and pelvic pain. (33) This highlights the fact that the use of DVR may be linked to increased rates of sexually transmitted infections if not used with other tools such as condoms. (23,61)

In contrast, some studies have shown that younger women are likely to have higher adherence to similar tools if they perceive that they are at high risk of HIV infection. (69) Therefore, implementing well-tailored personalized support, providing education about the perceived benefits of PrEP to this population, facilitating access to trusted healthcare providers, and accommodating

lengthy trials to create room for empowerment on the tool could improve adherence within this age group. (70)

On the other hand, older age was found to be associated with being adherent to the DVR, irrespective of the existing known factors that limit adherence among young women. This comparatively high adherence may exist due to women's prior knowledge of related products such as the Dapivirine levonorgestrel ring, NuvaRing®, and the female condom, (71,72) as well as the independence they have over their health matters. Also, some studies have found that despite high adherence among older women, some still purposefully remove the ring. (73) Factors that lead to such removal include discomfort during use/sex, concerns of harm, a doctor's request, not on a salary-based income, rumors about sickness and infertility. (74,75) Evidence from another continent suggests that $\frac{3}{4}$ of women at menopause had perfect adherence to the ring. (76) In this scenario, women preferred the ring because it was easy to use and did not interfere with erection. (76) Thus, one might conclude a better adherence to the ring in this age group as compared to others, which needs, though not yet, to be studied in Africa.

Chapter 4: Summary of Methodological Issues, Future Directions, and Review Conclusions.

In this chapter, we have covered the strengths and limitations that are directly linked to the conduct of this comprehensive methodological study. We further narrated the implications that the study findings have, and a conclusion to the study results.

4.1. Strengths and Limitations

The strengths of this systematic review and meta-analysis lie in the breadth of the search, the novelty of the research question, the analytical methods, and the narrative synthesis of factors associated with DVR adherence. Most limitations of our review originate from the underlying evidence. These include not being able to pool all studies conducted in Africa to date due to data availability, leading to the inability to conduct a subgroup. The risk of bias was low for most studies. There was a serious moderate heterogeneity. This could be attributed to differences in study designs, dosing in mother studies or trials, and other clinical characteristics. We employed a random effects model that correctly accounted for heterogeneity, however, we suggest caution when interpreting these results.

4.2. Future Directions Based on Study Findings

Given the findings of this study, there is a need to advance implementation research to determine circumstances that would help users adhere to the ring above the current rates. This could mean resizing the ring to limit the chance of partners feeling the ring during sexual intercourse and advancing the ring's life span to limit it being user-dependent. Even though some findings already exist on young women, (45) these are not sufficient to capture specifics on adherence among young women in Africa. Given the already known low adherence within this population, as well as the differences in risky health behaviors (7) that may exist across the 54 African states, (77) it is

essential to investigate uptake and adherence within this population in a diversified context. Furthermore, there is a need to consider strategies to subsidize costs related to the use of the ring, especially for young people whose income levels often affect their use and adherence to sexual and reproductive health services and tools such as DVR. (8,9) Additionally, a standardized method to capture adherence should be employed for all studies being carried out. This would help in the effective evaluation of findings and a better understanding of implementation strategies. Furthermore, there is a need for study adherence across different categories of women, including those at menopause. By capturing a wide and similar population across the globe, there would be room for a comprehensive comparative evaluation of DVR adherence worldwide, providing guidelines for implementation. The unavailability of data and inability to use some of the already published findings in their current format require advanced methods such as Individual Patient Meta-analysis to help better explain factors associated with DVR and reasons behind the considerable level of heterogeneity between studies.

4.3. Conclusion

Our study is the most comprehensive review of the level of DVR adherence and associated factors. In agreement with most studies, DVR adherence is lower in younger individuals. The overall adherence to DVR is suggested to be high, though with very low certainty of evidence. Approaches that promote adherence while limiting side effects, such as sexually transmitted infections, and implementation research targeting women with different characteristics, including those at menopause, are needed. Particularly, Individual Patient Data Meta-analysis will provide more meaningful DVR adherence. These findings suggest that DVR should not be used as a sole tool for HIV prevention, as the certainty of evidence for adherence was generally low.

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Appendixes:

1. Data Search

Summary of search and strategy Dapivirine

MEDLINE	45
Embase	98
CINAHL	17
Global Health	17
Google Scholar	40
Subtotal	217
-duplicates	-105
Total	112

- 1.
2. Used Africa filter by Pienaar, E., Grobler, L., Busgeeth, K., Eisinga, A. and Siegfried, N. (2011), Developing a geographic search filter to identify randomised controlled trials in Africa: finding the optimal balance between sensitivity and precision. Health Information & Libraries Journal, 28: 210-215. <https://doi.org/10.1111/j.1471-1842.2011.00936.x>
- 3.
4. September 10, 2024
5. MEDLINE (OVID)
6. Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
7. Search Strategy:
8. -----
9. 1 dapivirine.mp. (304)
10. 2 (aids 105293 or aids105293 or r 147681 or r147681 or tmc 120 or tmc120).mp. (33)
11. 3 (DPVVR or DPV-VR).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (3)
12. 4 or/1-3 (322)
13. 5 (therapy or regimen or intervention or PrEP or prophyla*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (7032056)
14. 6 4 and 5 (193)
15. 7 (adheren* or complian*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (435275)

16. 8 6 and 7 (74)
17. 9 Africa.mp. or exp Africa/ (408587)
18. 10 (Africa* or Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Canary Islands or Cape Verde or Central African Republic or Chad).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (409064)
19. 11 (Comoros or Congo or Democratic Republic of Congo or Djibouti or Egypt or Equatorial Guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea Bissau or Ivory Coast or Cote d'Ivoire or Jamahiriya or Jamahiriya or Kenya or Lesotho or Liberia or Libya or Libia).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (310725)
20. 12 (Madagascar or Malawi or Mali or Mauritania or Mauritius or Mayote or Morocco or Mozambique or Mocambique or Namibia or Niger or Nigeria or Principe or Reunion or Rwanda or Sao Tome or Senegal or Seychelles or Sierra Leone or Somalia or South Africa or St Helena or Sudan or Swaziland).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (207502)
21. 13 (Tanzania or Togo or Tunisia or Uganda or Western Sahara or Zaire or Zambia or Zimbabwe or Central Africa or Central African or West Africa or West African or Western Africa or Western African or East Africa or East African or Eastern Africa or Eastern African or North Africa or North African or Northern Africa or Northern African or South African or Southern Africa or Southern African or subSaharan Africa or subSaharan African).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (139410)
22. 14 or/9-13 (829957)
23. 15 ("guinea pig" or "guinea pigs" or "aspergillus niger").tw. (107613)
24. 16 14 not 15 (722344)
25. 17 8 and 16 (45)
- 26.
27. Database: Embase <1974 to 2024 September 09>
28. Search Strategy:
29. -----
30. 1 dapivirine.mp. or dapivirine/ (923)
31. 2 (aids 105293 or aids105293 or r 147681 or r147681 or tmc 120 or tmc120).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer,

- drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (207)
32. 3 (DPVVR or DPV-VR).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (7)
 33. 4 or/1-3 (933)
 34. 5 (therapy or regimen or intervention or PrEP or prophyla*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (10981217)
 35. 6 4 and 5 (663)
 36. 7 (adheren* or complian*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (713214)
 37. 8 6 and 7 (246)
 38. 9 Africa.mp. or exp Africa/ (486815)
 39. 10 (Africa* or Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Canary Islands or Cape Verde or Central African Republic or Chad).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (495543)
 40. 11 (Comoros or Congo or Democratic Republic of Congo or Djibouti or Egypt or Equatorial Guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea Bissau or Ivory Coast or Cote d'Ivoire or Jamahiriya or Jamahiryia or Kenya or Lesotho or Liberia or Libya or Libia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (306300)
 41. 12 (Madagascar or Malawi or Mali or Mauritania or Mauritius or Mayote or Morocco or Mozambique or Mocambique or Namibia or Niger or Nigeria or Principe or Reunion or Rwanda or Sao Tome or Senegal or Seychelles or Sierra Leone or Somalia or South Africa or St Helena or Sudan or Swaziland).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (244424)
 42. 13 (Tanzania or Togo or Tunisia or Uganda or Western Sahara or Zaire or Zambia or Zimbabwe or Central Africa or Central African or West Africa or West African or Western Africa or Western African or East Africa or East African or Eastern Africa or Eastern African or North Africa or North African or Northern Africa or Northern African or South African or Southern Africa or Southern African or subSaharan Africa or subSaharan African).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (158444)
 43. 14 or/9-13 (935577)
 44. 15 ("guinea pig" or "guinea pigs" or "aspergillus niger").tw. (106803)
 45. 16 14 not 15 (828774)
 46. 17 8 and 16 (98)
 - 47.

48. CINAHL (EBSCO)

49.

Tue, September 10, 2024 2:09:23 PM

#	Query	Limiters/Expanders	Last Run Via	Results
S14	S8 AND S13	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	17
S13	S11 not S12	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	251,289
S12	TX ("guinea pig" or "guinea pigs" or "aspergillus niger")	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	2,935
S11	S9 OR S10	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	254,224
S10	TX (Africa* or Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Canary Islands or Cape Verde or Central African Republic or Chad) OR TX (Comoros or Congo or Democratic Republic of Congo or Djibouti or Egypt or Equatorial Guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	254,224

	Bissau or Ivory Coast or Cote d'Ivoire or Jamahiriya or Jamahiryia or Kenya or Lesotho or Liberia or Libya or Libia) OR TX (Madagascar or Malawi or Mali or Mauritania or Mauritius or Mayote or Morocco or Mozambique or Mocambique or Namibia or Niger or Nigeria or Principe or Reunion or Rwanda or Sao Tome or Senegal or Seychelles or Sierra Leone or Somalia or South Africa or St Helena or Sudan or Swaziland) OR TX (Tanzania or Togo or Tunisia or Uganda or Western Sahara or Zaire or Zambia or Zimbabwe or Central Africa or Central African or West Africa or West African or Western Africa or Western African or East Africa or East African or Eastern Africa or Eastern African or North Africa or North African or Northern Africa or Northern African or South African or Southern Africa or Southern African or subSaharan Africa or subSaharan African)			
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S9	(MH "Africa+") OR "Africa"	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	113,990
S8	S6 AND S7	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	19
S7	TX (adheren* or complian*)	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	170,250
S6	S4 AND S5	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	34
S5	TX (therapy or regimen or intervention or PrEP or prophyla*)	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	2,440,393
S4	S1 OR S2 OR S3	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	79
S3	TX (DPVVVR or DPV-VR)	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1
S2	TX (aids 105293 or aids105293 or r147681 or r147681 or tmc 120 or tmc120)	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	3

S1	"dapivirine"	Search modes - Proximity	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	77
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- 50.
- 51.
52. Global Health (OVID)
53. Database: Global Health <1973 to 2024 Week 36>
54. Search Strategy:
55. -----
56. 1 dapivirine.mp. [mp=abstract, title, original title, broad terms, heading words, cabicodes words] (128)
57. 2 (aids 105293 or aids105293 or r 147681 or r147681 or tmc 120 or tmc120).mp. [mp=abstract, title, original title, broad terms, heading words, cabicodes words] (20)
58. 3 (DPVVR or DPV-VR).mp. [mp=abstract, title, original title, broad terms, heading words, cabicodes words] (3)
59. 4 or/1-3 (141)
60. 5 (therapy or regimen or intervention or PrEP or prophyla*).mp. [mp=abstract, title, original title, broad terms, heading words, cabicodes words] (750036)
61. 6 4 and 5 (74)
62. 7 (adheren* or complian*).mp. [mp=abstract, title, original title, broad terms, heading words, cabicodes words] (77878)
63. 8 6 and 7 (34)
64. 9 Africa.mp. or exp Africa/ (303458)
65. 10 (Africa* or Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Canary Islands or Cape Verde or Central African Republic or Chad).mp. [mp=abstract, title, original title, broad terms, heading words, cabicodes words] (340738)
66. 11 (Comoros or Congo or Democratic Republic of Congo or Djibouti or Egypt or Equatorial Guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea Bissau or Ivory Coast or Cote d'Ivoire or Jamahiriya or Jamahiryia or Kenya or Lesotho or Liberia or Libya or Libia).mp. [mp=abstract, title, original title, broad terms, heading words, cabicodes words] (115659)
67. 12 (Madagascar or Malawi or Mali or Mauritania or Mauritius or Mayote or Morocco or Mozambique or Mocambique or Namibia or Niger or Nigeria or Principe or Reunion or Rwanda or Sao Tome or Senegal or Seychelles or Sierra Leone or Somalia or South Africa or St Helena or Sudan or Swaziland).mp. [mp=abstract, title, original title, broad terms, heading words, cabicodes words] (137499)
68. 13 (Tanzania or Togo or Tunisia or Uganda or Western Sahara or Zaire or Zambia or Zimbabwe or Central Africa or Central African or West Africa or West African or Western Africa or Western African or East Africa or East African or Eastern Africa or Eastern African or North Africa or North African or Northern Africa or Northern African or South African or Southern Africa or Southern African or subSaharan Africa or subSaharan African).mp. [mp=abstract, title, original title, broad terms, heading words, cabicodes words] (281861)
69. 14 or/9-13 (374416)

- 70. 15 ("guinea pig" or "guinea pigs" or "aspergillus niger").tw. (19612)
- 71. 16 14 not 15 (354804)
- 72. 17 8 and 16 (17)
- 73.
- 74. GoogleScholar
- 75. allintitle: Dapivirine adherence OR compliance
- 76. Yields 40

2. Characteristics of Excluded Studies

Characteristics	Studies
Ongoing studies	(46,47)
Outcome not adherence	(39,78,79)
Qualitative and commentary studies	(75,80)
Duplicates of the abstract	(81,82)
Abstracts	(79,83–93)
Secondary studies of the included studies	(37,94–97)
Duplicate of wrong outcome	(98)