South African National Essential Medicine List
Primary Healthcare Medication Review process
Component: HIV and AIDS

EVIDENCE REVIEW

Title: To determine if the dapivirine eluting vaginal ring (dapivirine) is safe and effective in preventing HIV acquisition in women at substantial risk of HIV infection

Date: 9 June 2022

Key findings

- We conducted a search for systematic reviews of randomized controlled trials, and guidelines to determine whether the dapivirine eluting vaginal ring is safe and effective in preventing HIV acquisition in women at substantial risk of HIV infection.
- We identified two systematic reviews– both pooled data from two randomised controlled trials (RCTS) of dapivirine versus placebo – the Ring and ASPIRE studies.
- Data from the two placebo controlled RCTs informed the 2021 World Health Organization (WHO) Guideline recommendations for use of dapivirine vaginal ring in HIV prevention. On AGREE assessment, the 2021 WHO guidelines scored favourably (6/7), and GRADE-adolopment was performed.
- Use of the dapivirine ring may reduce HIV incidence compared to non-use (23 fewer HIV acquisitions per 1000 patient, 95% CI 10-34 fewer acquisitions, moderate quality evidence), and is not associated with an increase in adverse events (RR 1.02, 95% CI 0.98-1.06).However one RCT found 94 instances of social harm in 4680 person-years of follow-up, of which 93% were partner-related.
- We found no RCTS comparing dapivirine to tenofovir plus emtricitabine, which is the current standard of care for prevention of HIV acquisition in South Africa.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Based on this evidence review, the PHC/Adult hospital level committee suggests not to use the dapivirine ring as an additional option for prevention of HIV acquisition in women.
Rationale: Available evidence for the dapivirine ring is restricted to placebo-controlled data, with no studies comparing dapivirine to oral tenofovir plus emtricitabine, the current standard of care in South Africa. There is currently no data for efficacy in adolescents. The dapivirine ring cannot be used in pregnancy. There is sub-group of women who cannot use tenofovir plus emtricitabine for whom the dapivirine ring may be an option. However, at the current proposed price, dapivirine is unaffordable. The estimated threshold price for reviewing this recommendation is R52.00 per ring.
Level of Evidence: Moderate quality of evidence
Review indicator: Reduction in price

NEMLC RECOMMENDATION (23 JUNE 2022):
The NEMLC accepted the proposed PHC/Adult Hospital Level ERC recommendation with amendments to the review indicator (added, uptake and social harms), as follows:
Review indicator: Reduction in price; Uptake of all PrEP; Social harms of all PrEP

Monitoring and evaluation considerations: see review indicators above

Research priorities: see review indicators above

(Refer to Appendix 2 for the Evidence to decision framework)

1. Executive Summary

Date: 6 June 2022
Medicine (INN): Dapivirine vaginal ring
Medicine (ATC): G01AX17
Indication (ICD10 code): Z29.2
Patient population: Women > 18 years of age
Incidence: Estimated 140 000 new infections in women aged 15 and over in South Africa. The HIV incidence per 1000 population is 7.79 (UNAIDS country factsheet, South Africa). Incidence in women has decreased between 2014 and 2017 from 4.9 to 3.1 seroconversion events per 100 person-years but remains high (Vandormael).
Level of Care: Primary healthcare
Prescriber Level: Nurse prescriber
Current standard of Care: Oral tenofovir plus emtricitabine
Efficacy estimates: A meta-analysis of 2 phase III placebo-controlled trials of 4588 women found a 29% reduction of HIV acquisition risk (95% CI 11 to 43%; I^2 = 0%; moderate certainty evidence). 23 fewer women per 1000 using the dapivirine vaginal ring would acquire HIV infection compared to placebo (95% CI: from 34 fewer to 10 fewer), NNT 48 (95% CI 28 to 160) (Obiero).
Motivator/reviewer name(s): Regina Osih, Jeremy Nel, Halima Dawood, Hasina Subedar, Lise Jamieson, Trudy Leong
PTC affiliation: Jeremy Nel - Helen Joseph Hospital PTC; Halima Dawood – KZN Provincial PTC

2. Authors, affiliation and conflict of interest details:

1) Regina Osih –The Aurum Institute
2) Jeremy Nel – University of the Witwatersrand
3) Halima Dawood – Gray's Hospital, University of KwaZulu-Natal
4) Hasina Subedar – PrEP Programme Manager, National Department of Health
5) Lise Jamieson – Health Economics and Epidemiology Research Office (HE^2RO), University of Witwatersrand
6) Trudy Leong – Essential Drugs Programme, National Department of Health

RO, JN, HD, HS, LJ and TL have no interests to declare pertaining to dapivirine vaginal ring.

3. Introduction/ Background

South Africa has one of the world's highest prevalence and incidence of HIV. There were 230,000 newly infected adults with HIV in 2020, of which 140,000 were women aged 15 and over. The HIV incidence per year per 1000 population in adults aged 15-49 was estimated at 7.79. Women aged 15-49 were estimated to have a prevalence of 24.7% and women aged 15-24 a prevalence of 10.4% (range 4.0-16.4). While combination prevention modalities such as oral PrEP are available, accessibility to additional prevention modalities may assist in reducing HIV acquisition, particularly in adolescent young girls and women.

The dapivirine vaginal ring is a microbicide that inhibits HIV replication. Duration of action is 3 months. Dapivirine acts locally in the reproductive tract mucosa to prevent HIV replication (Baeten).

There are no head-to-head comparisons of dapivirine to oral PrEP (fixed-dose combination of tenofovir plus emtricitabine). Oral PrEP is the current standard of care recommended for those at high risk of acquiring HIV (PHC STGs and EML, 2020). Compared to placebo/ no PrEP, oral PrEP reduces risk of HIV infection by 51% (95% CI 33% to 73%) (Fonner). Poor adherence resulted in decreased effectiveness of oral PrEP. When stratified by mode of acquisition, oral PrEP showed similar effectiveness across groups: Oral PrEP vs placebo RR of 0.34 (95%CI 0.15 to 0.80) for rectal exposure and RR of 0.54 (95% CI 0.32 to 0.90) for penile/vaginal exposure. Notably, oral PrEP had decreased efficacy in individuals <25 years old, which may be the result of poorer adherence: RR 0.71 (95%CI 0.47 to 1.06). Emergence of tenofovir or emtricitabine resistance was low, and there was no evidence for oral PrEP resulting in risk compensating behavior (NEMLC report, 2017-9 review).

Comparing direct medicine prices, dapivirine is more expensive than oral PrEP, at a proposed price of $14.96/ R213.11 (Direct communication from NDoH Programme) and from a local public sector perspective, the service delivery would

generally be the same for both interventions. However, cost-effectiveness analyses suggest that dapivirine is cost-effective compared to oral PrEP – the latter requiring HIV, creatinine clearance and hepatitis B surface antigen tests; whilst the dapivirine vaginal ring only requires HIV-testing (Smith, WHO July 2021). South African studies found that amongst female sex workers in KwaZulu-Natal, dapivirine would be cost-saving (Glabius) and that the dapivirine vaginal ring could have a modest impact on the HIV epidemic and be a cost-effective intervention, despite low efficacy, if uniform coverage across all high-risk groups was achieved (Reidy).

Furthermore, a systematic review found that the use of dapivirine was highly acceptable, and the vast majority of participants across studies reported that the rings are easy to insert and remove (Griffin).

Pregnant and postpartum women, in particular, have higher rates of HIV acquisition compared with non-pregnant women (Drake, Kinuthia, Thomson), but there are no published studies in pregnant women to date. Two studies will provide more data on the dapivirine ring in pregnancy and breastfeeding mothers: B-PROTECTED (MTN-043) has completed follow-up and results are awaited, the DELIVER study is currently underway (MTN-042).

In March 2022, the South African Health Products Regulatory Authority approved the use of the dapivirine ring in women aged 18 years and above. Thus, an evidence review was conducted to inform a recommendation by the National Essential Medicines List Committee.

4. Purpose/Objective:
Should the dapivirine vaginal ring be used for HIV prevention among women at substantial risk of HIV infection?

PICO eligibility criteria*(Adapted from PICO question 1, "Should the dapivirine vaginal ring vs. non-use of the dapivirine vaginal ring be used for HIV prevention among women at substantial risk of HIV infection?", that informed the WHO Guidelines, July 2021):*

Population	Women at substantial risk of HIV infection (defined as HIV incidence of >3 per 100 person–years in the absence of PrEP
Intervention	Dapivirine vaginal ring
Comparator	No intervention
Outcome	HIV infection; Any adverse event; Any grade 3/4 adverse event; Drug resistance; Contraceptive effectiveness; Pregnancy-related adverse events; Therapeutic/elective abortion; Number of sexual partners , measured pre- to post-intervention; Condom use at last sex act , measured pre- to post-intervention
Studies	Systematic reviews of randomised controlled trials.

Note: The WHO guideline development PICO did not include oral PrEP tenofovir plus emtricitabine as comparator

5. Methods:
We sourced World Health Organization (WHO) guidelines and appraised these using the AGREE 2 tool (Brouwers - https://www.agreetrust.org/agree-ii/), to determine if the GRADE-adolpment approach could be used for efficiency purposes. This approach to guideline production combines adoption, adaptation, and, as needed, de novo development of recommendations (Schünemann), using the WHO Clinical Guidelines' Panel's evidence to decision framework.

TL also conducted a search for systematic reviews of randomised controlled trials in two databases on 4 May 2022 to determine if there was any new evidence that had not been included in the WHO guidelines.

a. Data sources: Epistemonikos and PUBMED were searched.

b. Search strategy: See appendix I.

6. Results:
Guidelines:
The recent WHO Consolidated guidelines on HIV prevention, testing, Treatment, service Delivery and monitoring: Recommendations for a Public Health approach of July 2021 was identified as providing updated guidance on the

dapivirine vaginal ring as a prevention option (WHO, July 2021). These guidelines were appraised using the AGREE2 instrument (Brouwers). Refer to appendix 2, for the AGREE2 assessment conducted by JN and TL (See appendix 2).

WHO Consolidated guidelines on HIV prevention, testing, Treatment, service Delivery and monitoring: Recommendations for a Public Health approach, July 2021.

Citation (date published)	Recommendation (pg)	AGREE II appraisal
WHO Consolidated guidelines on HIV prevention, testing, Treatment, service Delivery and monitoring: Recommendations for a Public Health approach, July 2021.	Pg 6. The dapivirine vaginal ring may be offered as an additional prevention choice for women at substantial risk[a] of HIV infection as part of combination prevention approaches. ***(Conditional recommendation, moderate certainty evidence)*** a. Substantial risk of HIV infection is defined as HIV incidence greater than 3 per 100 person–years in the absence of PrEP.	**6/7**

Appendix 3 describes the evidence profile (GRADE tables for the dapivirine ring review of evidence, 17 September 2020) that informed the WHO Guideline recommendations.

Systematic reviews:

A search for systematic reviews in two databases was conducted to identify additional evidence that was not included in the July 2021 WHO guidelines. The same 4 systematic reviews (Musekiwa, Obiero, Lokken, Ridgeway) was retrieved from both databases. These systematic reviews were screened by one reviewer (TL) and three were excluded for synthesis – see table 1 for the list of excluded studies. One systematic review was selected for inclusion in this review (Obiero) confirmed by another reviewer (RO). Table 2 describes the details of the selected Cochrane review (Obiero).Two RCTs included in that systematic review informed the WHO guidelines –the Ring Study (IPM-027) (Nel) and ASPIRE (MTN-020) (Baeten) trials.

Effects of intervention

- *Risk of acquiring HIV infection*

The Cochrane review included 12 RCTs of various microbicides for the prevention of sexually transmitted infection with 32,464 participants, conducted in Sub-Saharan Africa, of which two compared dapivirine to placebo. The review found that dapivirine reduces the risk of acquiring HIV infection (55 HIV acquisitions per 1000 women) compared to placebo (78 per 1000), risk ratio (RR) 0.71, (95% confidence interval (CI) 0.57 to 0.89, I^2 = 0%, 2 trials, 4588 women; *moderate-certainty evidence*. Overall, the two included RCTs investigating dapivirine ring were assessed as low risk of bias (using the Cochrane 'Risk of bias' tool), but the quality of evidence was downgraded by one level for imprecision, due to lack of optimal information size. Similarly, the risk of publication bias could not be evaluated, as there were too few trials.

An age-stratified analysis of the ASPIRE study (Baeten) found that the dapivirine ring did not reduce HIV incidence among women aged <25 years (10%, 95% CI -41 to 43) and reduced HIV incidence by 61% (95% CI 32 to 77) among women aged ≥ 25 years. The age stratified analysis in the Ring Study (Nel) found no significant difference in efficacy of the dapivirine ring amongst women aged ≤21 years [Hazard ratio (HR) 0.85; 95% CI 0.45 to 1.60] compared to women >21 years (HR 0.63; 95% CI, 0.41 to 0.97).

- *Serious adverse events*

The review found no difference between dapivirine ring and placebo in terms of serious adverse events (288/2620 vs 216/1968, RR 1.12 (95% CI 0.94 to 1.32); I^2 = 87%; *low certainty evidence.* Quality of the evidence was assessed as low due to imprecision, lack of optimal information size as well as inconsistency.

- *Adverse event – social harm*

The ASPIRE RCT reported on study-related social harm, defined as "non-medical adverse consequences of dapivirine vaginal ring use or of trial participation more generally" (Palanee-Philips). They found 94 instances of social harm with 4680 person-years of follow-up, of which 93% (n=87) were partner-related. 61% (n=85) had disclosed study participation to their primary partners. 40% of the cases of social harm were categorized as having a more than

minimal impact on the quality of life. Younger women (18–26 years) were more than twice as likely to experience social harm than older women, resulting in decreased product adherence.

Conclusion

The WHO Guidelines (WHO, July 2021) recommends inclusion of dapivirine as part of a comprehensive combination prevention approach, providing women the choice between oral PrEP (TE) and dapivirine ring options. Moderate certainty evidence suggests that there will be 23 fewer HIV acquisitions per 1000 patient using dapivirine ring compared to no ring, 95% CI 10-34 fewer acquisitions. However, there is concern that the ring might not be as effective in younger women (<25 years), a key demographic in South Africa. Further research will be required to determine if the low efficacy seen in younger women is due to lower adherence or additional factors.

There are no head-to-head comparisons of the dapivirine ring to oral PrEP. However, a larger reduction in HIV acquisition was seen for oral PrEP compared to placebo than has been seen with dapivirine (Obiero, Fonner).

Table 1: List of excluded studies

Study		Reason for exclusion
1	Musekiwa A, Fernando NB, Abariga SA. Effectiveness of vaginal microbicides in preventing HIV transmission. Trop Med Int Health. 2020 Jul;25(7):790-802. doi: 10.1111/tmi.13401	Duplicate of Cochrane review (Obiero, 2021)
2	Lokken EM, Mathur A, Bunge KE, Fairlie L, Makanani B, Beigi R, et al. Pooled Prevalence of Adverse Pregnancy and Neonatal Outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results From a Systematic Review and Meta-Analyses to Inform Trials of Novel HIV Prevention Interventions During Pregnancy. Front Reprod Health. 2021;3:672446.	PICO eligibility criteria not met
3	4. Ridgeway K, Montgomery ET, Smith K, Torjesen K, van der Straten A, Achilles SL, Griffin JB. Vaginal ring acceptability: A systematic review and meta-analysis of vaginal ring experiences from around the world. Contraception. 2022 Feb;106:16-33.	PICO eligibility criteria not met (may be relevant when assessing the evidence to decision framework criteria)

Table 2: Characteristics of the included study

Citation	Study design	Population	Intervention vs comparator	Outcomes	Effect sizes	Comments
• ***Systematic review:***						
Obiero J et al, 2021. Topical microbicides for preventing sexually transmitted infections (Review). Cochrane Database Syst Rev. 2021 Mar 13;3(3):CD007961. [8]	Systematic Review and Meta-Analysis	12 studies; 32 464 participants (12 trials conducted in sub-Saharan Africa, with one having a study site in the USA, and another a site in India) **Note: The population specific to the dapivirine vaginal ring was 4 588 women from 2 RCTs.** Eligible participants were sexually active non-pregnant heterosexual women.	**Intervention:** Dapivirine (2 RCTs, n=4588), **Comparator:** Placebo	**Primary outcomes:** • Risk of acquiring HIV infection – incidence of laboratory-confirmed HIV • Serious adverse events	**Dapivirine vs placebo:** *Risk of acquiring HIV infection:* 55 per 1000 vs 78 per 1000; RR 0.71 (95% CI 0.57 to 0.89); I^2=0%; NNT *(moderate certainty evidence)* *Serious adverse events:* There was no clear evidence of a difference between dapivirine vaginal ring vs placebo: 288/2620 vs 216/1968; RR 1.12 (95% CI 0.94 to 1.32); I^2 = 87% *(low certainty evidence)* No studies assessed the acceptability of the intervention.	• There is a concern that only two RCTs have to date assessed dapivirine vaginal ring. Thus, the certainty of evidence for risk of acquiring HIV infection was downgraded one level, from high to moderate certainty for imprecision, due to lack of optimal information size. • *Risk of bias:* Overall assessment described in the Cochrane review – **LOW RISK** ○ Random sequence generation (selection bias) – **LOW RISK** ○ Allocation concealment (selection bias) – **LOW RISK** ○ Blinding of participants and personnel (performance bias) – **LOW RISK** ○ Blinding of outcome assessment (detection bias) – **LOW RISK** ○ Incomplete outcome data (attrition bias) – **LOW RISK** ○ Selective reporting (reporting bias) – **LOW RISK** ○ Other bias – **LOW RISK**

Table 3: WHO Guideline Panel's GRADE tables for the dapivirine ring review of evidence (17 September 2020)

Author(s): Fonner V. & Dalglish S.
Question: The dapivirine vaginal ring compared to non-use of the dapivirine vaginal ring for HIV prevention among women at substantial risk of HIV infection
Setting: Global
Bibliography: One phase II placebo-controlled RCT, two phase III placebo-controlled RCTs, two open-lapel extension studies (see references for detailed information)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DVR	No DVR	Relative (95% CI)	Absolute (95% CI)		
HIV infection (RCTs) (follow up: 24 months)												
2	RCTs[a,b]	serious[c]	not serious	not serious	not serious	none	151/2610 (5.8%)	155/1952 (7.9%)	RR 0.71 (0.57 to 0.88)	**23 fewer per 1,000** (from 34 fewer to 10 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
HIV infection (DREAM) (follow up: 12 months)												
1	Observational study[d]	serious[e]	not serious	not serious	serious[b]	dose response gradient[f]	1.8 per 100 person years (95% CI: 1.1-2.9)g	4.7 per 100 person years (95% CI: 3.7-5.8)h	reduction in incidence 0.62 (-- to --) [i]	not estimable	⊕⊕⊕◯ Moderate	CRITICAL
HIV infection (HOPE) (follow up: 12 months)												
1	Observational study[j]	not serious[k]	not serious	not serious	not serious	dose response gradient[f]	2.7 per 100 person years (95% CI: 1.9-3.8)[l]	4.4 per 100 person years (95% CI: 3.2-5.8)[m]	reduction in incidence 0.39 (0.14 to 0.65)	not estimable	⊕⊕⊕◯ Moderate	CRITICAL
Any adverse event (RCTs) (follow up: 24 months)												
1	RCT[a]	serious[n]	not serious	not serious	not serious	none	1322/2619 (50.5%) [o]	739/1968 (37.6%) [o]	RR 1.02 (0.98 to 1.06)	**8 more per 1,000** (from 8 fewer to 23 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Any adverse event (safety study) (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DVR	No DVR	Relative (95% CI)	Absolute (95% CI)		
1	RCT	not serious	not serious	not serious	not serious	none	114/140 (81.4%) [p]	121/140 (86.4%) [p]	RR 0.9 (0.9 to 1.0)	**86 fewer per 1,000** (from 86 fewer to 0 fewer)	⨁⨁⨁⨁ High	IMPORTANT
Any grade 3/4 adverse event (RCTs) (follow up: 24 months)												
2	RCTs[a]	serious[n]	serious[q]	not serious	not serious	none	236/2619 (9.0%)	204/1968 (10.4%)	RR 1.19 (0.68 to 2.05)	**20 more per 1,000** (from 33 fewer to 109 more)	⨁⨁◯◯ Low	CRITICAL
Drug resistance (RCTs) (follow up: 24 months)												
2	RCTs[a]	serious[b]	not serious	not serious	serious[r]	none	22/145 (15.2%) [s]	19/152 (12.5%) [s]	RR 1.13 (0.64 to 2.01)	**16 more per 1,000** (from 45 fewer to 126 more)	⨁⨁◯◯ Low	CRITICAL
Pregnancy-related adverse events (in ASPIRE and The Ring Study) (follow up: 24 months)[u]												
2	RCTs	serious[b]	not serious	serious[v]	very serious[r]	none	Range of effects [w]		not estimable	not estimable	⨁⨁⨁◯ Very low	CRITICAL
Number of sexual partners (self-reporting ≥2 sexual partners), measured pre- to post-intervention (follow up: 24 months)[x]												
1	RCT	not serious	not serious	not serious	serious[r]	none	64/107 (59.8%) [y]	74/132 (56.1%) [y]	**p**-value comparing pre to post 0.814 (-- to --)	not estimable	⨁⨁⨁◯ Moderate	IMPORTANT
Condom use at last sex act (self-reported), measured pre- to post-intervention (follow up: 24 months)[x]												
1	RCT	not serious	not serious	not serious	serious[r]	none	37/107 (34.6%) [z]	46/132 (34.8%) [z]	not estimable	not estimable	⨁⨁⨁◯ Moderate	IMPORTANT

CI=Confidence interval; RCT= randomised controlled trial; RR= risk ratio

Explanations

a. Pooled effect size from two Phase III RCTs (ASPIRE and the Ring Study), random effects meta-analysis.

b. Both ASPIRE and The Ring Study identified sites with lower than anticipated participant adherence to the study product. In ASPIRE, the sample size was recalibrated to allow for a fully-powered analysis

excluding individuals from the two sites with lower than expected adherence. Enrollment at the two sites was stopped but participants already enrolled were allowed to continue in follow-up. Results for the primary endpoint—HIV infection—are presented with and without data from the two sites. For this outcome, we included results inclusive of all sites (i.e., the more conservative estimate). In The Ring Study, three sites were identified with high levels of protocol noncompliance and low adherence. As a result, prior to unblinding all participants from these sites were withdrawn from the study, resulting in approximately 20% attrition. For these reasons we have downgraded for potential risk of bias.

c. Outcomes from one Phase I/II safety study included (Nel et al., 2016). Intent-to-treat analysis.

d. DREAM was a Phase IIIB multicenter follow-on open-label extension study (prospective cohort design). Participants included those who had completed the Ring Study and were HIV-negative at enrollment. In DREAM, willingness to use the dapivirine vaginal ring (DVR) was a requirement for study participation.

e. HIV-1 incidence in DREAM was compared descriptively with the incidence rate obtained from bootstrap sampling in the placebo group of The Ring Study (i.e., a simulated control group was used to estimate incidence among those not receiving the DVR). Although the lack of a true control is a limitation of the study design, this was not considered a serious risk of bias, thus results were not downgraded.

f. Both open-label extension studies, HOPE and DREAM, found significantly higher DVR adherence (as measured objectively through levels of residual dapivirine in used rings) as compared with the placebo-controlled RCTs that preceded them (ASPIRE and the Ring Study, respectively). Additionally, both OLEs found higher effectiveness than in the RCTs. Given that we have not downgraded the evidence for any other reason, and both studies found a dose-response relationship, we have upgraded the evidence one-level.

g. 18 HIV infections occurred in the study cohort among participants using DVR in the modified intent to treat analysis (n=938). Of note, 26 HIV infections occurred overall, but only 18 were included in analysis (3 were excluded due to HIV infection at baseline; 3 had positive HIV-1 antibody tests at the exit visit but were HIV-1 RNA negative at the last product visit (LPUV, thus considered to have become infected after DVR discontinuation; one participant with HIV-1 seroconversion at the exit visit had an HIV-1 RNA result below the limit of detection (<40 copies/mL) at the LPUV, and an undetectable result when retested. The remaining participant seroconverted after prolonger non-DVR use (5 months). A sensitivity analysis including the participant who seroconverted after prolonged non-DVR use and the participant with an HIV-1 RNA result below the limit of detection at LPUV, demonstrated an incidence rate of 2·0 (95% CI: 1.1-2.9 per 100 person years), a 57% reduction in incidence.

h. This simulated incidence rate was calculated from bootstrap sampling of participants in the placebo group of The Ring Study, matched for research center, age, and presence of sexually transmitted infections (STIs) at enrolment.

i. Confidence interval not provided.

j. HOPE was a Phase IIIB multicenter follow-on open-label extension study (prospective cohort design). Participants included those who had completed the ASPIRE study and were HIV-negative at enrollment. In HOPE, ring use was optional (women could choose at every visit whether or not to accept the ring).

k. HIV-1 incidence in HOPE was compared descriptively with the incidence rate obtained from bootstrap sampling in the placebo group of ASPIRE (i.e., a simulated control group was used to estimate incidence among those not receiving the DVR). Although the lack of a true control is a limitation of the study design, this was not considered a serious risk of bias, thus we did not downgrade the results.

l. Overall 35 HIV infections occurred out of 1456 participants.

m. This simulated incidence rate was calculated from bootstrap sampling of participants in the placebo group of ASPIRE, matched for research center, age, and presence of a curable sexually transmitted infections (STIs) at baseline.

n. Both ASPIRE and The Ring Study identified sites with lower than anticipated participant adherence to the study product. In ASPIRE, the sample size was recalibrated to allow for a fully-powered analysis excluding individuals from the two sites with lower than expected adherence. Enrollment at the two sites was stopped but participants already enrolled were allowed to continue in follow-up. In The Ring Study, three sites were identified with high levels of protocol noncompliance and low adherence. As a result, prior to unblinding all participants from these sites were withdrawn from the study, resulting in approximately 30% attrition. For these reasons we have downgraded for potential risk of bias.

o. Outcomes reported as treatment emergent adverse events for the Ring Study (defined as adverse events that occurred/worsened after the first insertion of IP, up to 6 weeks after last ring use)(Nel et al., 2016). For ASPIRE (Baeten et al., 2016), outcome reported as “primary safety endpoint” defined as “any serious adverse event, any grade 3 or 4 adverse event, and any grade 2 adverse event”. Analysis includes results from all 15 sites, including those with low adherence.

p. Outcome reported as treatment-emerge adverse events (defined as AEs which occurred/worsened after the first insertion of IP, up to 6 weeks after last ring use)

q. Within the random effects meta-analysis, heterogeneity was high (I-squared=76.55%); reasons for the high heterogeneity are unknown, so the evidence was downgraded once for inconsistency.

r. Downgraded for imprecision due to the small number of events

s. Defined as any non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations

t. Of 2629 women enrolled, 2310 women returned for follow-up and reported using a hormonal contraceptive method at any point during study participation (1139 in the dapivirine arm, 1171 in the placebo arm). A total of 117 pregnancies occurred among 114 participants during use of a hormonal contraceptive method (63 pregnancies in the dapivirine ring arm and 54 in the placebo arm). Pregnancy incidence in the dapivirine arm versus placebo among women using injectable depot medroxyprogesterone acetate was 0.43% vs. 0.54%, among women using injectable norethisterone enanthate was 1.15% vs. 0%, among women using hormonal implants was 0.22% vs. 0.69%, and among women using oral contraceptive pills was 32.26% vs. 28.01%. Pregnancy incidence did not differ by study arm for any of the hormonal

contraceptive methods (individual hazard ratios for each contraception method are presented in Table 2 of Balkus et al., 2017).
u. Includes results from entire ASPIRE trial and site-specific results from The Ring Study (only site in South Western Uganda reporting results)
v. Downgraded for indirectness because outcomes were measured among women who were only exposed to the study product for a brief period during early pregnancy (all participants were regularly screened for pregnancy and study product was immediately discontinued once pregnancy was detected). Therefore, these results may be different if women had been exposed to the study product for the entire duration of their pregnancies.
w. A range of varying pregnancy outcomes were reported for ASPIRE and one research site in The Ring Study. These results are summarized in Table 7 of the report. Across studies, no significant differences in adverse pregnancy events were found, although women were only exposed to DVR in early pregnancy (see comment on indirectness).
x. Measured only in one research site (in South Western Uganda)
y. These numbers represents the total number of participants (recruited specifically from the research site in South West Uganda) reporting ≥2 sexual partners (time period not specified) at baseline (non-use of DVR) and 104 weeks follow-up (DVR). The p-value comparing baseline to follow-up rates of condom use at last sex was 0.814 (chi-square test).
z. These numbers represents the total number of participants (recruited specifically from the research site in South West Uganda) reporting condom use at last sex act at baseline (non-use of DVR) and 104 weeks followup (DVR). The p-value comparing baseline to follow-up rates of condom use at last sex was 0.706 (chi-square test).

Appendix 1 – Search strategy

Database: **Epistemonikos**
Date: **4 May 2022**

Search: (title:(dapivirine) OR abstract:(dapivirine))
Restricted to systematic reviews

4 records retrieved.

Database: **PubMed**
Date: **4 May 2022**

Search	Query	Results
#3	Search: (("dapivirine"[Supplementary Concept] OR "dapivirine"[All Fields] OR "dapivirine"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("prevent"[All Fields] OR "preventability"[All Fields] OR "preventable"[All Fields] OR "preventative"[All Fields] OR "preventatively"[All Fields] OR "preventatives"[All Fields] OR "prevented"[All Fields] OR "preventing"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields] OR "prevention s"[All Fields] OR "preventions"[All Fields] OR "preventive"[All Fields] OR "preventively"[All Fields] OR "preventives"[All Fields] OR "prevents"[All Fields])) AND (meta-analysis[Filter] OR systematicreview[Filter])	4
#2	Search: (("dapivirine"[Supplementary Concept] OR "dapivirine"[All Fields] OR "dapivirine"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("prevent"[All Fields] OR "preventability"[All Fields] OR "preventable"[All Fields] OR "preventative"[All Fields] OR "preventatively"[All Fields] OR "preventatives"[All Fields] OR "prevented"[All Fields] OR "preventing"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields] OR "prevention s"[All Fields] OR "preventions"[All Fields] OR "preventive"[All Fields] OR "preventively"[All Fields] OR "preventives"[All Fields] OR "prevents"[All Fields])) AND (systematicreview[Filter])	4
#1	Search: ("dapivirine"[Supplementary Concept] OR "dapivirine"[All Fields] OR "dapivirine"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("prevent"[All Fields] OR "preventability"[All Fields] OR "preventable"[All Fields] OR "preventative"[All Fields] OR "preventatively"[All Fields] OR "preventatives"[All Fields] OR "prevented"[All Fields] OR "preventing"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields] OR "prevention s"[All Fields] OR "preventions"[All Fields] OR "preventive"[All Fields] OR "preventively"[All Fields] OR "preventives"[All Fields] OR "prevents"[All Fields])	176

4 records retrieved, all duplicates of Epistemonikos search.

Appendix 2: Adaptation of the WHO 2020 TPT Guidelines Evidence to decision framework

(Note: Where judgements differed, both WHO and PHC/Adult Hospital Level's assessments have been described)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	• More than half of all new HIV infections globally are among women and girls.[1] • Approximately 7,000 young women aged 15–24 years become infected with HIV each week.[2] • 20.1 million women and girls are currently living with HIV.[1] • Young women aged 15–24 years are twice as likely to be living with HIV than men. • HIV is the global leading cause of death for women (15-49 years).[2] • Recent results from ECHO trial in sub-Saharan Africa demonstrate continued high HIV incidence among women (3.81 per 100 woman years (95% CI 3·45 to 4·21)), despite the availability of existing HIV prevention options, including oral pre-exposure prophylaxis (PrEP)).[3] • There are challenges with uptake and continued use of a daily pill i.e. oral PrEP among women. Alternatives to daily oral PrEP are needed. Having expanded options for PrEP would address users differing needs and preferences.[4 5] • This evidence demonstrates that additional HIV prevention options are needed for women and girls	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> South Africa has one of the world's highest prevalence and incidence of HIV. There were approximately 230,000 newly infected adults with HIV in 2020, of which 140,000 were women aged 15 and over. The HIV incidence per 1000 population in adults aged 15-49 is estimated at 7.79 Women aged 15-49 are estimated to have a prevalence rate of 24.7 with young women aged 15-24 having a prevalence of 10.4.	

[1] UNAIDS, . 20.1 million girls and women living with HIV. 2020.

[2] UNAIDS, . Women and HIV: A spotlight on adolescent girls and young women. 2019.

[3] Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. Lancet. 2019 Jul 27;394(10195):303-313. doi: 10.1016/S0140-6736(19)31288-7. Epub 2019 Jun 13. Erratum in: Lancet. 2019 Jul 27;394(10195):302.

[4] van der Straten A, Agot K, Ahmed K, Weinrib R, Browne EN, Manenzhe K, et al; TRIO Study Team. The Tablets, Ring, Injections as Options (TRIO) study: what young African women chose and used for future HIV and pregnancy prevention. J Int AIDS Soc. 2018 Mar;21(3):e25094. doi: 10.1002/jia2.25094.

[5] Montgomery ET, Beksinska M, Mgodi N, Schwartz J, Weinrib R, Browne EN, et al. End-user preference for and choice of four vaginally delivered HIV prevention methods among young women in South Africa and Zimbabwe: the Quatro Clinical Crossover Study. J Int AIDS Soc. 2019 May;22(5):e25283. doi: 10.1002/jia2.25283.

	Furthermore, pregnant and postpartum women, in particular, have higher rates of HIV acquisition compared with non-pregnant women.[6] [7] [8] As pregnant women are excluded from clinical trials, a systematic review by Lokken et al[9] demonstrated the background prevalence of adverse neonatal and pregnancy outcomes (Malawi, South Africa, Uganda, Zimbabwe). The outcomes with the highest pooled prevalence were preterm birth (12.7%, 95%CI 11.2–14.3), LBW (11.7%, 95%CI 10.6–12.9), and gestational hypertension (11.4%, 95%CI 7.8–15.7). Among the outcomes with the lowest pooled prevalence estimates were neonatal mortality (1.7%, 95%CI 1.4–2.1), pregnancy loss [1.9%, 95%CI 1.1–2.8, predominately studies (23/29) assessing losses occurring after the first trimester], PPROM (2.2%, 95%CI 1.5–3.2), and stillbirth (2.5%, 95%CI 2.2–2.7). The data would assist in investigating use of dapivirine ring in pregnancy	

Desirable effects: How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
WHO Guideline panel		
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	HIV infection •Pooled results from two phase III placebo-controlled randomized trials (ASPIRE[10] and the Ring Study[11]) **demonstrated a significant reduction in HIV incidence (29%, 95% CI: 11%-43%)** comparing women randomized to receive the dapivirine ring (DVR) vs. those randomized to receive a placebo ring. •An age-stratified analysis from one of the two placebo-controlled randomized trials (ASPIRE) found that **the dapivirine ring did not reduce HIV incidence among women aged <25 years and reduced HIV incidence by 61% among women aged ≥ 25 years**. The age stratified analysis in the Ring Study found **no difference in reduction in HIV incidence comparing women aged ≤21 years vs. >21 years.** •However, when results across the tool trials were pooled, **HIV-1 risk reduction was significantly higher in participants older than 21 years; no risk reduction was observed in participants 21 years or younger.[12]** •An analysis from ASPIRE assessed the relationship of product adherence, as measured by residual levels of dapivirine in returned study rings, and **found a significant relationship between adherence and efficacy.** Medium to high levels of adherence (defined as <22mg of residual dapivirine) was associated with a 65% relative reduction in HIV risk (95% CI: 22	DVR is not expected to prevent HIV from non-vaginal routes of HIV transmission, such as receptive anal intercourse (RAI) and parenteral transmission. One sub-analysis of data from ASPIRE found that RAI comprised only 1.5% of all sex acts reported over a three-month period. In the adjusted analysis, RAI was not associated with reduced HIV-1 protection from the ring.[15]

[6] Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. PLoS Med. (2014) 11:e1001608. doi: 10.1371/journal.pmed.1001608

[7] Kinuthia J, Drake AL, Matemo D, Richardson BA, Zeh C, Osborn L, et al. HIV acquisition during pregnancy and postpartum is associated with genital infections and partnership characteristics: a cohort study. AIDS. (2015) 29:2025–33. doi: 10.1097/QAD.0000000000000793

[8]Thomson K, Hughes J, Baeten J, John-Stewart G, Celum C, Cohen C, et al. Increased risk of HIV acquisition among women throughout pregnancy and during the postpartum period: a prospective per-coital-act analysis among women with HIV-infected partners. J Infect Dis. (2018) 218:16–25. doi: 10.1093/infdis/jiy113

[9] Lokken EM, Mathur A, Bunge KE, Fairlie L, Makanani B, Beigi R, Noguchi L, Balkus JE. Pooled Prevalence of Adverse Pregnancy and Neonatal Outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results From a Systematic Review and Meta-Analyses to Inform Trials of Novel HIV Prevention Interventions During Pregnancy. Front Reprod Health. 2021;3:672446. doi: 10.3389/frph.2021.672446.

[10] Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, et al.; MTN-020–ASPIRE Study Team. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. N Engl J Med. 2016 Dec 1;375(22):2121-2132. doi: 10.1056/NEJMoa1506110.

[11] Nel A, van Niekerk N, Kapiga S, Bekker LG, Gama C, Gill K, et al.; Ring Study Team. Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women. N Engl J Med. 2016 Dec 1;375(22):2133-2143. doi: 10.1056/NEJMoa1602046.

[12] Rosenberg, Z, Nel, A, van Niekerk, N, Van Baelen, B, Van Roey, J, Palanee-Phillips, T, Brown, E, Soto-Torres, L, Hillier, S, Baeten, J, Teams, IPM,027/The,Ring,Study,and,MTN-020/ASPIRE,Study, , , , . Pooled Efficacy Analysis of Two Phase III Trials of Dapivirine Vaginal Ring for the Reduction of HIV-1 Infection Risk in HIV-Uninfected Women in Sub-Saharan Africa . 2017

[15] Peebles K, van der Straten A, Palanee-Phillips T, Reddy K, Hillier SL, Hendrix CW, Harkoo I, Gati Mirembe B, Jeenarain N, Baeten JM, Brown ER; MTN-020/ASPIRE Study Team. Brief Report: Anal Intercourse, HIV-1 Risk, and Efficacy in a Trial of a Dapivirine Vaginal Ring for HIV-1 Prevention. J Acquir Immune Defic Syndr. 2020 Mar 1;83(3):197-201. doi: 10.1097/QAI.0000000000002253.

	to 84, p=0.01), low to high adherence levels (defined as <23.5mg of residual dapivirine) was associated with a relative risk reduction of 56% (95%CI: 20-76, p=0.007). Non-adherence (defined as ≥23.5 mg residual dapivirine) was not associated with a significant reduction in risk. • Results from two open-label extension projects (OLEs), HOPE and DREAM, which included women who participated in ASPIRE and the Ring Study, **demonstrated a range of effectiveness from 39% to 62% reduction in HIV incidence**, comparing HIV incidence among participants to a simulated control involving women randomized to the placebo arm of the prior randomized controlled trial, matched for STI, matched for research center, age, and presence of STIs at enrolment.[13] [14] **Both open-label extension projects noted increased adherence to DVR as compared with adherence to DVR measured during the randomized controlled trials.**	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> Furthermore, retrieved systematic reviews[16] [17] similarly pooled data from ASPIRE[6] and the Ring[7] RCTs showing that dapivirine ring significantly reduced HIV incidence (55 per 1000) compared to placebo (78 per 1000); RR 0.71 (95% CI 0.57 to 0.89, I^2 = 0%, n=4588 women; *moderate-certainty evidence*). Dapivirine vaginal ring was studied compared to placebo. Placebo-controlled oral PrEP (TE) studies suggest that oral PrEP may be more efficacious than the dapivirine ring: RR 0.49 (95% CI 0.33 to 0.73) but there are no head- to head comparative trials.	
Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**Adverse Events** • Results from a phase IIa safety study (n=140) **showed no increased risk of adverse events** comparing women randomized to the dapivirine ring vs. placebo ring.[18] • Pooled results from the two phase III trials, demonstrated **no increased risk for any adverse events** comparing women randomized to the dapivirine ring vs. placebo (relative risk= 1.02, 95% CI: 0.98 to 1.06) and **no increased risk for any grade 3 or 4 adverse event** comparing women randomized to the dapivirine ring vs. placebo (relative risk= 1.19, 95% CI: 0.68 to 2.05).[9, 10]	Given the vaginal ring provides a local delivery mechanism (i.e., dapivirine is delivered directly to the vaginal tissue), risk of systemic exposure is much lower than for oral therapies, thus reducing the potential for systemic toxicities (e.g., side effects and foetal complications).

[13] Baeten JM, Palanee-Phillips T, Mgodi NM, Mayo AJ, Szydlo DW, Ramjee G, et al.; MTN-025/HOPE Study Team. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. Lancet HIV. 2021 Feb;8(2):e87-e95. doi: 10.1016/S2352-3018(20)30304-0.

[14] Nel, A., van Niekerk, N., Van Baelen, B., Malherbe, M., Mans, W., Carter, A. , al., et. Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study. Lancet HIV. 2021 Feb;8(2):e77-e86. doi: 10.1016/S2352-3018(20)30300-3.

[16] Musekiwa A, Fernando NB, Abariga SA. Effectiveness of vaginal microbicides in preventing HIV transmission. Trop Med Int Health. 2020 Jul;25(7):790-802. doi: 10.1111/tmi.13401.

[17] Obiero J, Ogongo P, Mwethera PG, Wiysonge CS. Topical microbicides for preventing sexually transmitted infections. Cochrane Database Syst Rev. 2021 Mar 13;3(3):CD007961. doi: 10.1002/14651858.CD007961.pub3.

[18] Nel A, Bekker LG, Bukusi E, Hellström E, Kotze P, Louw C, et al. Safety, Acceptability and Adherence of Dapivirine Vaginal Ring in a Microbicide Clinical Trial Conducted in Multiple Countries in Sub-Saharan Africa. PLoS One. 2016 Mar 10;11(3):e0147743. doi: 10.1371/journal.pone.0147743.

	• One randomized controlled trial (ASPIRE) reporting on social harms (defined as "nonmedical adverse consequences of DVR use or of trial participation more generally") found **3% of women experienced a social harm during the trial.**[19] Younger women (aged 18-26) were over twice as likely to experience a social harm as compared to older women, and reporting a social harm was associated with short-term decreased product adherence. **Drug Resistance** • Across the two placebo-controlled trials, there was **no difference in the number of NNRTI mutations found among seroconverters comparing those randomized to DVR vs. placebo** (relative risk= 1.13, 95% CI: 0.64 to 2.01). [9, 10] **Contraceptive effectiveness and pregnancy outcomes** • **Note:** Use of effective contraception was part of the eligibility criteria across included studies. Additionally, women were tested for pregnancy at study visits, and use of study product was discontinued immediately following detection of pregnancy. • One analysis from ASPIRE evaluated contraceptive effectiveness, and **found no difference in pregnancy incidence comparing DVR to placebo arms, across all hormonal contraceptive methods.**[20] • Analyses from ASPIRE and The Ring Study (data from one specific research site) found **no significant differences in adverse pregnancy related events comparing DVR to placebo arms.** [21, 22] **Behavioral outcomes** • One research site from The Ring Study reported on condom use and sexual behavior (n=132) and **found no significant change in reports of non-condom use at last sex as reported at week 4 and week 104** (64% and 68%, respectively, p=0.71), and **no significant change in reports of 2 or more sexual partners comparing baseline and completion (week 104), p=0.81.**[23] • Studies found relatively high rates of curable STI incidence during the trials (at baseline and post-intervention) but **found no substantive differences comparing rates among those randomized to DVR vs. placebo.**[10] One sub-analysis from one research site in the Ring Study found significant decreases in diagnoses of Trichomonas vaginalis and Neisseria gonorrhea from baseline to 104 weeks followup. [17]	The reduced possibility for side effects and unlikely foetal toxicity might make DVR more acceptable to adolescent girls and young women. In comparison, oral PrEP has been associated with issues pertaining to bone mineral density, renal functioning, and a "startup syndrome" with associated gastrointestinal symptoms. None of these issues have been found with DVR.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Large ○ Moderate ○ Small ○ Trivial	As per WHO Guideline panel's rationale above.	

[19] Palanee-Phillips T, Roberts ST, Reddy K, Govender V, Naidoo L, Siva S, et al. Impact of Partner-Related Social Harms on Women's Adherence to the Dapivirine Vaginal Ring During a Phase III Trial. J Acquir Immune Defic Syndr. 2018 Dec 15;79(5):580-589. doi: 10.1097/QAI.0000000000001866.

[20] Balkus JE, Palanee-Phillips T, Reddy K, Siva S, Harkoo I, Nakabiito C, et al.. Brief Report: Dapivirine Vaginal Ring Use Does Not Diminish the Effectiveness of Hormonal Contraception. J Acquir Immune Defic Syndr. 2017 Oct 1;76(2):e47-e51. doi: 10.1097/QAI.0000000000001455.

[21] Kusemererwa, S., Abaasa, A.. Pregnancy incidence and outcomes among women using dapivirine vaginal ring for HIV prevention in a phase III clinical trial in south western Uganda. AIDS Research and Human Retroviruses; 2018.

[22] Makanani B, Balkus JE, Jiao Y, Noguchi LM, Palanee-Phillips T, Mbilizi Y, Moodley J, Kintu K, Reddy K, Kabwigu S, Jeenariain N, Harkoo I, Mgodi N, Piper J, Rees H, Scheckter R, Beigi R, Baeten JM. Pregnancy and Infant Outcomes Among Women Using the Dapivirine Vaginal Ring in Early Pregnancy. J Acquir Immune Defic Syndr. 2018 Dec 15;79(5):566-572. doi: 10.1097/QAI.0000000000001861.

[23] Kusemererwa, S., Abaasa, A.. Does the use of the dapivirine vaginal ring result in change in risk sexual behavior?. AIDS Research and Human Retroviruses; 2018.

○ Varies ○ Don't know		
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	• Mostly moderate certainty of evidence for HIV infection, adverse event outcomes, contraceptive effectiveness, and sexual behaviour outcomes. Mostly low certainty of evidence for outcomes related to drug resistance and adverse pregnancy-related outcomes. • Data available from 5 studies, including 3 RCTs and 2 observational studies. • RCTs had some risk of bias due to censoring of data at trial sites with low adherence. • OLEs used simulated controls, drawn from the placebo arm of the prior randomized studies, to estimate HIV incidence in the absence of ring use. • Approximately 5,000 participants across studies • Few absolute events for drug resistance and reproductive health outcomes (women taken off study product once pregnancy was known) • Data only available for women aged ≥18 years	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> All of the studies included South African sites. Follow-up studies exploring feasibility and acceptability and the open label extension study also took place in South Africa. However, it is unclear what efficacy is in women under 25, especially in a real-life setting that lacks the incentives and controls associated with clinical trials. **Note:** There is no available studies comparing dapivirine ring to oral PrEP (TE).	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	• HIV prevention and ring safety are highly valued across all stakeholders. • Women value having a discrete prevention option that they can choose to divulge to partners or not. • Any increase in drug resistance due to ring use would be an important consideration for population-level impact on treatment. However, due to the local delivery of dapivirine directly into vaginal tissue, risk of drug resistance for DVR appears to be less than for other PrEP delivery systems (i.e., oral PrEP) • There has been no noted behavioral risk compensation for oral PrEP among adolescent girls and young women. We do not know for certain if this will be the same for DVR use. However, we do know that many women who choose to use oral PrEP products also have difficulty using condoms consistently.	

• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> A systematic review[24]found favorable acceptability pooled prevalence of 85.6% (95%CI 81.3, 89.0). European (90.6%; 95%CI 83.9, 94.7), Asian (97.1%; 95%CI 92.0, 99.0), and multi-region studies (93.5%; 95%CI 84.6, 97.4) reported more favorable acceptability compared to African studies (59.4%; 95%CI 38.3, 77.5).	
Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	• Results from the systematic review and meta-analysis show that **the dapivirine ring has promising benefits regarding HIV prevention among women and few undesirable clinical effects.** • Results identified **no safety concerns of DVR, no evidence of increased drug resistance among seroconverters exposed to DVR, and no evidence of behavioral risk compensation.** Low levels of partner-specific social harms associated with ring use or trial participation were reported in one phase III RCT (ASPIRE). • **More research is needed to understand the use of and adherence to DVR among adolescent women and girls**, given that a pooled analysis of results from the two phase III placebo-controlled RCTs found no protective benefit of DVR among younger women aged ≤21 years. • **More research is needed to understand the effects of DVR among pregnant and lactating women** as DVR use within the reviewed studies was discontinued immediately following pregnancy detection and did not resume use until pregnancy and lactation had ceased. **A system is needed to capture adverse maternal and foetal/infant outcomes among pregnant and lactating women exposed to DVR** through links with pregnancy and anti-retroviral (ARV) registries.	Importantly, implementation of DVR across all trials was offered in the context of a comprehensive package of prevention services, including periodic HIV testing and counselling, risk reduction counselling, testing and treatment of sexually transmitted infections, antiretroviral treatment for HIV positive persons, access to free condoms, etc.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention *(compared to placebo)* ○ Favors the intervention ○ Varies ○ Don't know	As per WHO Guideline panel's rationale above. Compared to placebo, dapivirine ring shown to prevent HIV acquisition (RR 0.71; 95% CI 0.57 to 0.88). There are no head-to-head evidence for dapivirine ring. Oral PrEP appears to be more efficacious when compared to placebo in preventing HIV acquisition (RR 0.49; 95% CI 0.33 to 0.73). Of note, is that ASPIRE[19] reported on social harms (defined as "nonmedical adverse consequences of DVR use or of trial participation more generally") found 3% of women experienced a social harm during the trial. Younger women (aged 18-26) were over twice as likely to experience a social harm as compared to older women, and reporting a social harm was associated with short-term decreased product adherence.	There were no safety concerns, however, no benefit was found in women under 21 years which warrants further study.

[24] Ridgeway K, Montgomery ET, Smith K, Torjesen K, van der Straten A, Achilles SL, Griffin JB. Vaginal ring acceptability: A systematic review and meta-analysis of vaginal ring experiences from around the world. Contraception. 2022 Feb;106:16-33. doi: 10.1016/j.contraception.2021.10.001.

Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Medicine costs:** • According to the International Partnership for Microbicides, the **current cost of goods is $8 per ring**, with a total annual cost (12 rings) of $96. • Different modelling studies have estimated the total annual cost of DVR (inclusive of drug, laboratory costs and service delivery) is between $107-$115, with variation in cost by target group [25]; $131 (19); and between $152-$189(20), with variation by country. **Service delivery costs:** • Service delivery costs for ring use include routine HIV testing. A modeling study estimated the cost of HIV testing (assuming a negative result) to be $12 in the South African context.[26] Therefore, testing on a quarterly basis would involve a total cost of $48 annually, although this amount would vary by setting. • **DVR is expected to require fewer health system resources than oral PrEP**, as the only associated cost is HIV testing. Unlike oral PrEP, no creatinine monitoring or Hepatitis B testing is required for the dapivirine ring. Additionally, DVR may be suitable for delivery outside of clinic settings, such as using pharmacy, community, and self-care delivery models.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ **Large costs** ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	As per WHO Guideline panel's rationale above. Additional contextual information: According to the International Partnership for Microbicides, the **current cost of goods is $14.59 (per ring,** for the South African market (Communication from the NDoH Programme). Furthermore, the NDoH Programme considers that from a local public sector perspective, the service delivery would generally be the same for both dapivirine vaginal ring and oral PrEP. **Note:** The NDoH Programme advised that IPM provided an updated price of **$15.31** as of June 2022. Analysis conducted by the Health Economics and Epidemiology Research Office (HE^{2}RO), University of Witwatersrand, Johannesburg, using methods similar to their previous work on the costing of oral PrEP[27,28], **estimated the cost of provision of DVR at $130/woman initiated** (inclusive of drug, laboratory costs and service delivery), under the assumption that a	

[25] Smith J, Harris K, Garnett G, Van Damme L, Hallett, T. Cost-effectiveness of the intravaginal dapivirine ring: A modeling analysis. Topics in Antiviral Medicine; 2016.

[26] Glaubius R, Ding Y, Penrose KJ, Hood G, Engquist E, Mellors JW, Parikh UM, Abbas UL. Dapivirine vaginal ring for HIV prevention: modelling health outcomes, drug resistance and cost-effectiveness. J Int AIDS Soc. 2019 May;22(5):e25282. doi: 10.1002/jia2.25282.

[27] Jamieson L, Gomez GB, Rebe K, et al (2020) The impact of self-selection based on HIV risk on the cost-effectiveness of preexposure prophylaxis in South Africa. AIDS 34:883–891. https://doi.org/10.1097/QAD.0000000000002486

[28] Jamieson L, Johnson LF, Nichols BE, et al (2022) The Relative Cost-Effectiveness of Long-Acting Injectable Cabotegravir Versus Oral Pre-Exposure Prophylaxis: A Modelled Economic Evaluation and Threshold Analysis in South Africa Based on the HPTN 083 and 084 Trials. SSRN Journal. https://doi.org/10.2139/ssrn.4047136

	DVR client remains on the program for an average duration 5 months after initiation and the current cost of goods is $14.59/ring. Assuming a **coverage of 5% for 15 to 49-year-old women (coverage rates estimated based on the oral PrEP programme)**, we can expect a total of 528,000 to 575,000 women to take up DVR at a total cost of R999 to-R1,088 million (or $468-75 million) per year, over 2023 to 2027, assuming the cost of the ring remains at $14.59 per ring. The estimated threshold price for DVR to be as cost-effective as oral PrEP, was estimated as R52.00 per ring. **Refer to the short-report: Cost-effectiveness of dapivirine ring compared to oral PrEP, 23 May 2022.**	

Certainty of evidence of required resources: What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
o Very low o Low o Moderate o High o No included studies	Cost of resource requirements would vary by setting.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
o Very low o **Low** o Moderate o High o No included studies	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> Resource requirements would depend significantly on both the cost of the dapivirine ring and eventual uptake once rolled out. Though the assumed coverage/uptake was 5%, this was based on uptake seen in the oral PrEP programme. Uptake of the dapivirine ring, once available, remains uncertain.	

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention	Our review identified three studies related to the cost-effectiveness of the dapivirine vaginal ring: • Smith et al., 2018 (modeling study based in the South African context): **DVR would be a cost-effective intervention**, even with low efficacy, if its use was highly targeted to those at greatest risk (sex workers, young women and those with multiple partners). Glaubius et al., 2017 (modeling study based in the South African context): **DVR would be a cost-saving intervention for KwaZulu Natal if the intervention were prioritized for female sex workers.**	Prioritizing ring use for women at substantial risk of HIV infection will be critical. Attention on how to identify women at substantial risk, generate demand for DVR, and support adherence will be of utmost importance.

○ Varies ○ No included studies	• Reidy et al., 2019[29] (modeling study based on scenarios in Kenya, South Africa, Uganda, Zimbabwe): Use of the GOALS model found the **impact of DVR on HIV epidemics to be highly variable** and dependent on many factors, such as treatment coverage and potential intervention cost. **The cost per HIV infection averted varied between $13,000 and $121,000 within the South African context.** • Studies highlighted uncertainty regarding **adherence to DVR and demand for/uptake of DVR** as critical aspects of determining cost effectiveness and impact.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ **Favors the comparison** *(compared to SOC: oral PrEP - TE)* ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studie	**Contextual information** **DVR compared to oral daily Prep (TE):** Over a 20-year time horizon (2023-2042), **daily oral PrEP is estimated to be more cost effective compared to DVR**, over a baseline with no PrEP: at $13,445/HIV infection averted (oral PrEP), versus both DVR effectiveness assumptions (29%: $60,707/HIV infection averted and 62%: $26,549/HIV infection averted). For DVR to be similarly cost-effective to oral PrEP**, the cost of the ring will need to be lower at approximately $4/ring** (assuming 29% effectiveness of DVR) **and up to $8.80/ring** (assuming 62% effectiveness of DVR). This is based on analysis conducted by HE^{2}RO comparing the cost-effectiveness of scaling up DVR vs daily oral PrEP, modelling the impact of each intervention in a HIV transmission model, and assessing incremental cost per HIV infection averted. Main assumptions included the same target population (women aged 15-49 and female sex workers), the same target coverage (5%), and the same average duration of use (5 months), for both DVR and oral PrEP. They modelled two scenarios for effectiveness for DVR protection against HIV infection: 1) 29%, and 2) an upper limit of 62%. In comparison the effectiveness of oral PrEP is estimated at 65% [30].	

Equity: What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	• DVR offers an **additional, discrete, woman-controlled biomedical HIV prevention option.** • Expanding PrEP options through offering DVR in addition to oral PrEP **could help meet the diverse needs and preferences of women**. • Evidence from the field of contraception has demonstrated an association between increased contraceptive choice and increased contraceptive use among women. **Increasing biomedical HIV prevention options could have a similar effect (i.e., increased options may lead to increased use).**[31] • Access to the dapivirine ring for women could also provide **additional opportunities for sexual and reproductive health services**.	It is possible that offering DVR in addition to oral PrEP would replace oral PrEP use (e.g., oral PrEP users would switch to DVR or vice versa), but is also possible that offering DVR in addition to oral PrEP would expand PrEP use more generally by providing options and allowing preferable selection.

[29] Reidy M, Gardiner E, Pretorius C, Glaubius R, Torjesen K, Kripke K. Evaluating the potential impact and cost-effectiveness of dapivirine vaginal ring pre-exposure prophylaxis for HIV prevention. PLoS One. 2019 Jun 26;14(6):e0218710. doi: 10.1371/journal.pone.0218710.
[30] Fonner VA, Dalglish SL, Kennedy CE, et al (2016) Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS 30:1973–1983. https://doi.org/10.1097/QAD.0000000000001145
[31] Ross J, Stover J. Use of modern contraception increases when more methods become available: analysis of evidence from 1982-2009. Glob Health Sci Pract. 2013 Jul 26;1(2):203-12. doi: 10.9745/GHSP-D-13-00010.

	• **Cost of dapivirine ring and clinic visits could prevent some people from gaining access**. However, current cost estimates suggest PrEP delivered through a vaginal ring would cost less than oral PrEP. • **Preventing HIV in high incidence female populations will reduce future treatment cost.** • **Preventing HIV infection among women will help sustain their health and that of their sexual partners.**	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ **Varies** ○ Don't know	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> For those women who cannot use SOC (TE), accessing dapivirine ring will promote equity for PrEP. Current cost estimates reviewed by the WHO Guideline panel suggests that PrEP delivered through a vaginal ring would cost less than oral PrEP. However, comparing direct medicine prices, dapivirine is more expensive than oral PrEP, at a proposed price of $15.31 (Direct communication from NDoH Programme) and from a local public sector perspective, the service delivery would generally be the same for both interventions.	

Acceptability: Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	A comprehensive systematic review and meta-analysis assessing global acceptability of vaginal rings (agnostic to active pharmacological ingredient) found that rings were highly acceptable. **The overall acceptability (proportion of women reporting a favorable experience) across 46 studies and 19,080 was 87.4% (95% CI: 83.5% to 90.5%)**. This review also found that most women who used the ring liked it, whereas hypothetical acceptance was low among women who had no direct experience.[32] • An additional systematic review on vaginal rings focused in low- and middle-income countries that included 68 RCTs and observational studies also found high acceptability, and the **vast majority reported the ring was easy to insert and remove**. Most women disclosed ring use to partners, although some women feared violence or anger from partners if ring use was discovered. Ring acceptability increased over time, both as women got used to using the ring and as the ring became popularized in their community. **Women expressed preferences for devices that were easily accessible, long-acting, and partner-approved that could prevent both HIV infection and pregnancy and that could also be used without the partner's awareness, with minimal impact on sex, and with few side effects**.[33] • A systematic review specific to DVR including 21 studies, all with a geographic focus in sub-Saharan Africa, found similar high acceptability. **The review also noted that partner influence can affect ring use and that perceived community awareness and acceptance of the ring was important.** [34]	.

[32] Ridgeway K, Montgomery ET, Smith K, Torjesen K, van der Straten A, Achilles SL, Griffin JB. Vaginal ring acceptability: A systematic review and meta-analysis of vaginal ring experiences from around the world. Contraception. 2022 Feb;106:16-33. doi: 10.1016/j.contraception.2021.10.001.

[33] Griffin JB, Ridgeway K, Montgomery E, Torjesen K, Clark R, Peterson J, Baggaley R, van der Straten A. Vaginal ring acceptability and related preferences among women in low- and middle-income countries: A systematic review and narrative synthesis. PLoS One. 2019 Nov 8;14(11):e0224898. doi: 10.1371/journal.pone.0224898.

[34] Schwartz K , Bhavaraju N , Ridgeway K , Gomez A. End-user perspectives on their ability, motivation and opportunity to use the dapivirine vaginal ring. AIDS 2020; 2020.

	• Thirty citations on acceptability were found through current search, the vast majority of which related to ASPIRE, the Ring Study, DREAM, or HOPE, in addition to acceptability outcomes reported in the included phase II safety study. As found in the other reviews, **DVR was highly acceptable among women with experience using the product.**	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
o No o Probably no o Possibly/Probably yes o Yes o Varies o Don't know	As per WHO Guideline panel's rationale above.	

Feasibility: Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
o No o Probably no o Probably yes o Yes o Varies o Don't know	• **Multiple studies of the dapivirine vaginal ring have been conducted, thus proving its feasibility across a variety of trial settings**. In addition to the safety study, two phase III RCTs, and two open-label extension projects included in this review of the evidence, additional safety studies have been successfully conducted among adolescent young women in the United States, post-menopausal women in the United States, and among healthy women in Europe. [35, 36, 37] • **DVR is relatively easy to transport and store**. It does not require refrigeration and can be stored at room temperature.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
o No o Probably no o Probably yes o Yes o Varies o Don't know	As per WHO Guideline panel's rationale above. Dapivirine ring is SAHPRA registered and can be implemented using the existing NDoH Programmatic infrastructure.	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	9 June 2022	RO, JN, HD, HS, LJ, TL	Dapivirine ring not be included in the EML. May be considered for sub-group, where standard of care (TE) cannot be used if the price per ring decreased to R52.00 per ring. Available evidence is restricted to placebo-controlled data.

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Short report: Cost-effectiveness of dapivirine ring compared to oral PrEP

Date: 23 May 2022
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Declaration of Interest: LJ (Health Economics and Epidemiology Research Office (HE^{2}RO), University of Witwatersrand) has no interests pertaining to dapivirine vaginal ring.

SUMMARY

Summary Table. Cost-effectiveness comparison of dapivirine ring (DVR) vs standard of care (oral PrEP)

	Dapivirine ring analysis		
	Oral PrEP	Dapivirine ring	
		29% effectiveness	*62% effectiveness*
Incremental cost per HIV infection averted (2023-2042)			
USD	$13,445	$60,707	$26,549
ZAR	R196,393	R886,741	R387,800
Incremental cost per life year saved (2023-2042)			
USD	$4,741	$19,985	$9,337
ZAR	R69,250	R291,912	R136,378
Budget impact (2023-2027)			
Number on intervention per year	529,000-577,069	528,000-575,000	528,000-575,000
Cost per year, ZAR	R565-616 million	R999-1,088 million	R1,001-1,091 million
Threshold price for DVR to be as cost-effective as oral PrEP, ZAR			
	-	R52	R107

Modelling assumptions:
- Baseline: no PrEP
- Effectiveness: 65% (oral PrEP); 29%-62% (DVR)
- Average duration on PrEP: 5 months (oral PrEP); 5 months (DVR)
- Populations targeted: women aged 15-49, female sex workers
- Coverage: 5% across target population

Cost assumptions:
- Provision of dapivirine ring, total cost = R1,892 (incl cost of ring $14.59/R213.11 per ring)
- Provision of oral PrEP, total cost = R1,067 (incl cost of TDF/FTC R68.65/month)
- 3-monthly visits for both oral PrEP and dapivirine ring

Oral PrEP is a more cost-effective intervention in comparison to the dapivirine ring owing to the higher effectiveness and lower cost. Current price estimate for the dapivirine ring to enter the South African market is set at $14.59/ring, or R213.11/ring. For DVR to be as cost-effective as oral PrEP, it would need to cost substantially less at R52/ring (under a 29% effectiveness assumption) up to R107/ring (under a 62% effectiveness assumption).

FULL REPORT

Methods

- ***Modelling and assumptions***

The impact of PrEP (oral PrEP, dapivirine ring) on the HIV epidemic was estimated using the Thembisa model (version 4.4), a deterministic compartmental HIV transmission model of the South African HIV epidemic (Johnson and Dorrington 2021).

Oral PrEP effectiveness, accounting for both efficacy and adherence, was assumed to be 65% for women (Fonner et al. 2016). *Dapivirine ring effectiveness* was assumed to be 29% based on the pooled results from two phase III placebo-controlled randomized trials, ASPIRE and the ring study (Baeten et al. 2016; Nel et al. 2016). A second scenario was included to model an effectiveness estimate of 62%, the upper limit estimate from two open-label extension projects (OLEs), HOPE and DREAM (Baeten et al. 2021; Nel et al. 2021).

- ***Costs***

Costs were estimated from the provider perspective, the South African government. All costs are presented in both 2021 South African Rand (ZAR) and United States Dollar (USD), and uninflated. In addition, we present the numbers of women on dapivirine ring and the total cost for the next 5 years to inform the health budget.

An ingredients-based approach was used to estimate the average cost of oral PrEP (TDF/FTC) and dapivirine ring provision, using data from PrEP demonstration sites and subsequent implementation programmes, as well as following current PrEP guidelines. Full methodology for the estimation of oral PrEP cost has been described elsewhere (Jamieson et al. 2020). The cost of dapivirine ring provision was structured using similar methodology; however, we adjusted the ingredients to include the dapivirine ring, additional professional nurse time for the initial insertion of the ring at initiation, and removed laboratory monitoring tests which are not required (e.g. ALT, creatinine testing, which are included in the oral PrEP costs).

In line with standard of care PrEP, visits are scheduled 3-monthly under both the oral PrEP and dapivirine ring scenarios.

The cost of oral PrEP is set at $4.70/month (R68.65/month, based on a tender price; Master Procurement Circular January 2021; using the average 2021 exchange rate of 14.61 ZAR = 1 USD). *The cost of one dapivirine ring* (for a month) is set at $14.59/ring, or R213.11/ring (IPM price, as per NEMLC review).

- ***Scenarios***

We modelled the provision of PrEP to women aged 15-49 years, including to female sex workers, scaling up coverage to 5% across target populations for both interventions (oral PrEP, dapivirine ring). Based on data from the South African PrEP implementation programme, the average duration on oral PrEP is estimated to be 5 months (Johnson and Dorrington 2021). We assumed the same duration for women initiating on the dapivirine ring, as a best guess as no implementation data outside of a trial setting is available.

We estimated cost-effectiveness as cost per HIV infection averted and cost per life year saved over a 5- and 20-year time horizon (2023-2027 and 2023-2042), over a *baseline of no PrEP*, but including currently available HIV interventions in South Africa (e.g. high coverages for condom provision, HIV testing services, and medical male circumcision). This allows us to determine the impact of a reduction in HIV incidence due to oral PrEP and the dapivirine ring on the need for subsequent ART, in addition to existing prevention interventions. The estimation of the cost of the HIV programme followed the same methodology as the South African HIV Investment Case.

- ***Threshold* analysis**

Anticipating a lower cost-effectiveness of the dapivirine ring due to a higher cost of the ring, and lower effectiveness, compared to oral PrEP, we conduct a threshold analysis on the price to estimate the price level at which the dapivirine ring is similarly cost-effective compared to oral PrEP.

Results

Table 1. Estimated cost of dapivirine and ring oral PrEP provision, per person initiated

	Dapivirine ring			Oral PrEP		
	Cost (USD)	***Cost (ZAR)***	***%***	***Cost (USD)***	***Cost (ZAR)***	***%***
Drugs	88	1,279	68%	28	412	37%
Labs	7	98	5%	16	235	21%
Consumables	0.5	7	0.3%	1	21	3%
Staff	27	394	21%	19	280	29%
Overheads	8	114	6%	8	120	11%
Total Cost	**130**	**1,892**		**73**	**1,067**	

The cost of provision of dapivirine ring and oral PrEP was estimated at $130 and $73 per woman initiated, respectively, for the average duration of 5 months after initiation, that they are in the PrEP programme (Table 1).

Table 2a. Impact and cost-effectiveness of dapivirine ring and oral PrEP over a 5- and 20-year time horizon (2021 USD)

		Dapivirine ring		
	Baseline	*29% effectiveness*	*62% effectiveness*	Oral PrEP
5-year time horizon (2023-2027)				
Total Cost of the HIV programme (USD, billions)	10.04	10.40	10.39	10.24
Incremental cost (USD, billions)	-	352 (4%)	350 (3%)	195 (2%)
Total new HIV infections (thousands)	0.91	0.91	0.90	0.90
HIV infections averted (thousands)	-	5.5 (1%)	13.6 (1%)	14.3 (2%)
Total life years lost to AIDS (millions)	11.39	11.39	11.39	11.39
Life years saved (thousands)	-	0.5 (0.004%)	6 (0.1%)	7 (0.1%)
Incremental cost per HIV infection averted (USD)	**-**	***63,477***	***25,859***	***13,637***
Incremental cost per life year saved (USD)	**-**	***693,612***	***58,204***	***29,853***
20-year time horizon (2023-2042)				
Total Cost of the HIV programme (USD, billions)	41.40	43.05	43.00	42.25
Incremental cost (USD, billions)	-	1,650 (4%)	1,598 (4%)	850 (2%)
Total new HIV infections (millions)	2.94	2.91	2.88	2.88
HIV infections averted (thousands)	-	27 (1%)	60 (2%)	63 (2%)
Total life years lost to AIDS (millions)	36.02	35.94	35.85	35.84
Life years saved (thousands)	-	83 (0.2%)	171 (0.5%)	179 (0.5%)
Incremental cost per HIV infection averted (USD)	**-**	***60,707***	***26,549***	***13,445***
Incremental cost per life year saved (USD)	**-**	***19,985***	***9,337***	***4,741***

Table 2b. Impact and cost-effectiveness of dapivirine ring and oral PrEP over a 5- and 20-year time horizon (2021 ZAR)

		Dapivirine ring		
	Baseline	*29% effectiveness*	*62% effectiveness*	Oral PrEP
5-year time horizon (2023-2027)				
Total Cost of the HIV programme (ZAR, billions)	146.71	151.85	151.83	149.56
Incremental cost (ZAR, billions)	-	5.1 (4%)	5.1 (3%)	2.8 (2%)
Total new HIV infections (thousands)	0.91	0.91	0.90	0.90
HIV infections averted (thousands)	-	5.5 (1%)	13.6 (1%)	14.3 (2%)
Total life years lost to AIDS (millions)	11.39	11.39	11.39	11.39
Life years saved (thousands)	-	0.5 (0.004%)	6 (0.1%)	7 (0.1%)
Incremental cost per HIV infection averted (ZAR)	**-**	***927,197***	***377,720***	***199,193***
Incremental cost per life year saved (ZAR)	**-**	***10,131,497***	***850,183***	***436,056***
20-year time horizon (2023-2042)				
Total Cost of the HIV programme (ZAR, billions)	604.68	628.79	628.03	617.10
Incremental cost (ZAR, billions)	-	24.1 (4%)	23.3 (4%)	12.4 (2%)
Total new HIV infections (millions)	2.94	2.91	2.88	2.88
HIV infections averted (thousands)	-	27 (1%)	60 (2%)	63 (2%)
Total life years lost to AIDS (millions)	36.02	35.94	35.85	35.84
Life years saved (thousands)	-	83 (0.2%)	171 (0.5%)	179 (0.5%)
Incremental cost per HIV infection averted (ZAR)	**-**	***886,741***	***387,800***	***196,393***
Incremental cost per life year saved (ZAR)	**-**	***291,912***	***136,378***	***69,250***

Over a 20-year time horizon, oral PrEP is estimated to be more cost effective, at $13,445/HIV infection averted, compared to the dapivirine ring under both 29% effectiveness ($60,707/HIV infection averted) and 62% effectiveness ($26,549/HIV infection averted) (Table 2a). Similar conclusions are reached under the 5-year time horizon analysis, and for incremental cost per life year saved. Note, the incremental cost per life year saved is substantially higher in the 5-year time horizon analysis as the effects of AIDS deaths have not yet been realized in the short time frame.

Results in ZAR are shown in Table 2b.

Table 3. Cost estimates for budget, years 2022/23 to 2026/27

	2022/23	2023/24	2024/25	2025/26	2026/27
Number of dapivirine ring clients	528,259	535,369	547,638	561,056	575,189
Total cost of dapivirine ring (USD, millions)	68	69	71	73	75
Total cost of dapivirine ring (ZAR, millions)	999	1,013	1,036	1,061	1,088

Assuming a coverage rate of 5% for 15-49-year-old women, we can expect a total of 528,000 to 575,000 women to take up the dapivirine ring at a cost of R999-R,1088 million (or $68-75 million) per year, over the next 5 years and assuming the cost of the ring remains at $14.59 or R213.11 per ring and women remain on the dapivirine ring for an average of 5 months.

Table 4. Threshold analysis: estimated price at which the dapivirine ring remains as cost-effective as oral PrEP

Solving for		***29% effectiveness***	***62% effectiveness***
Incremental cost/HIV infection averted			
	USD	$3.33	$7.33
	ZAR	R49	R107
Incremental cost/life year saved			
	USD	$3.54	$7.35
	ZAR	R52	R107

The estimated price at which the dapivirine ring becomes similarly cost-effective compared to oral PrEP would be $3.54/ring (if assuming 29% effectiveness) and ~$7.35/ring (if assuming 62% effectiveness).

Conclusion

Assuming the same duration and coverage between the PrEP interventions and the same target population, oral PrEP is more cost-effective than the dapivirine ring. This is mostly due to both the higher effectiveness (65% for oral PrEP vs 29% for dapivirine ring) and the lower cost per month of provision ($73 or R1,067 per woman initiated for oral PrEP vs $130 or R1,892 per woman initiated for dapivirine ring).

If the dapivirine ring achieves a consistent 62% effectiveness, it will still be less cost-effective compared to oral PrEP, as long as the price remains higher than $7.35/ring. A lower effectiveness of the dapivirine ring will result in the lower price per ring required in order to meet the same level of cost-effectiveness compared to oral PrEP.

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