



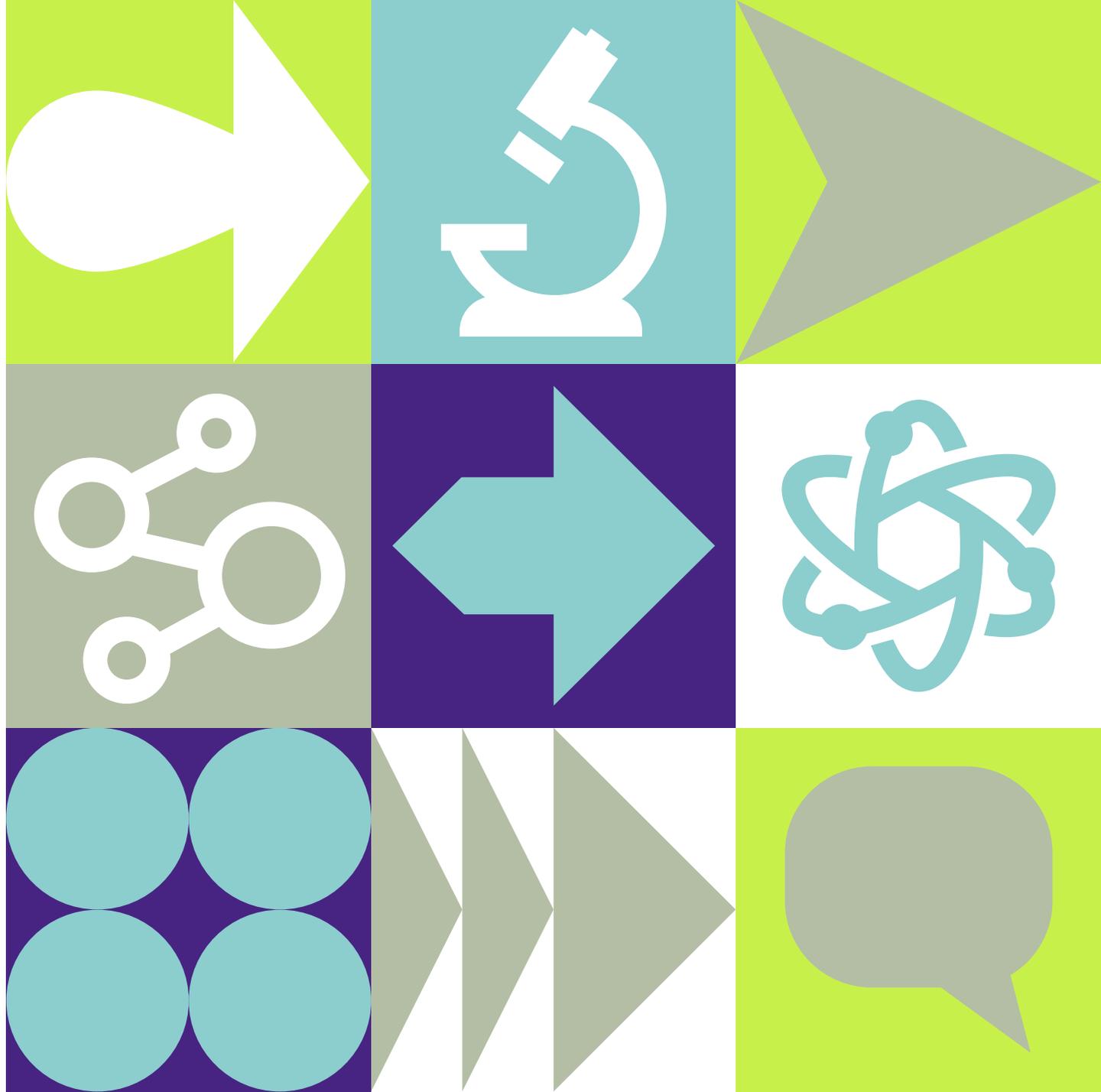
IAS 2021

**Intravaginal options:
WHO, EMA and other
regulatory approvals - where
we are**

Meg Doherty

Director, WHO Global HIV, Hepatitis and STIs
Programmes, Geneva

21 July 2021



Meg Doherty

WHO, EMA and other regulatory approvals - where we are



I have no
conflicts of
interest to
disclose





Evolution of WHO PrEP recommendations and guidance

HIV/AIDS Programme

PrEP for SDC, MSM & TG (**conditional** rec in the context of demo projects)

GUIDANCE ON PRE-EXPOSURE ORAL PROPHYLAXIS (PrEP) FOR SERODISCORDANT COUPLES, MEN AND TRANSGENDER WOMEN WHO HAVE SEX WITH MEN AT HIGH RISK OF HIV: Recommendations for use in the context of demonstration projects

July 2012

2012

MODULE 1 CLINICAL

WHO IMPLEMENTATION TOOL FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) OF HIV INFECTION

JULY 2017

2017 Imp tool

TECHNICAL BRIEF

WHAT'S THE 2+1+1?

EVENT-DRIVEN ORAL PRE-EXPOSURE PROPHYLAXIS TO PREVENT HIV FOR MEN WHO HAVE SEX WITH MEN: UPDATE TO WHO'S RECOMMENDATION ON ORAL PrEP

JULY 2019

2019 ED-PrEP

WHO Model List of Essential Medicines

2017

2014

PrEP for MSM (**strong** rec)

Other KP (**conditional** rec)

no recommendation for PWID

GUIDELINES

CONSOLIDATED GUIDELINES ON HIV PREVENTION, DIAGNOSIS, TREATMENT AND CARE FOR KEY POPULATIONS

JULY 2014

2014

2015

PrEP for people at substantial HIV risk (≈ 3 per 100PY) (**strong** rec)

GUIDELINES

GUIDELINE ON WHEN TO START ANTIRETROVIRAL THERAPY AND ON PRE-EXPOSURE PROPHYLAXIS FOR HIV

SEPTEMBER 2015

2015

2021 DPV-VR

WHO recommends the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection

2. CLINICAL GUIDELINES: ANTIRETROVIRAL DRUGS FOR HIV PREVENTION

2.1 The dapivirine vaginal ring

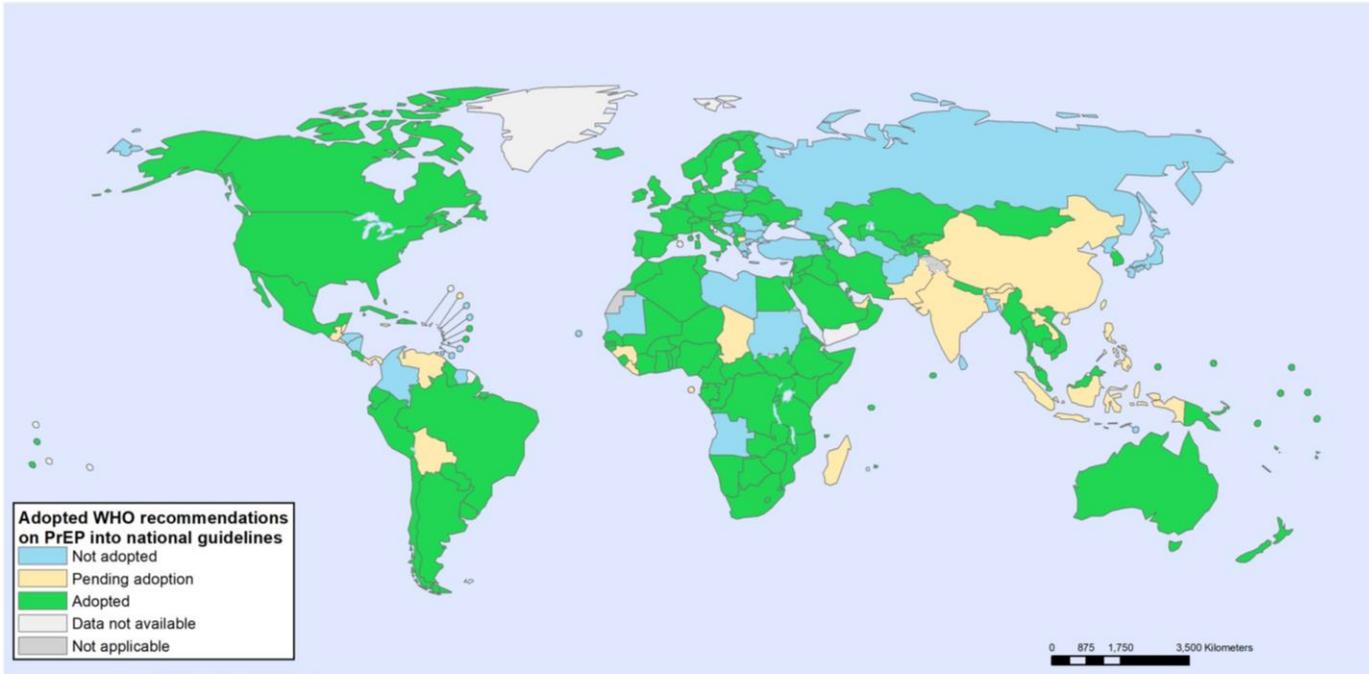
Recommendation

The dapivirine vaginal ring may be offered as an additional prevention choice for women.

2021 DPV-VR

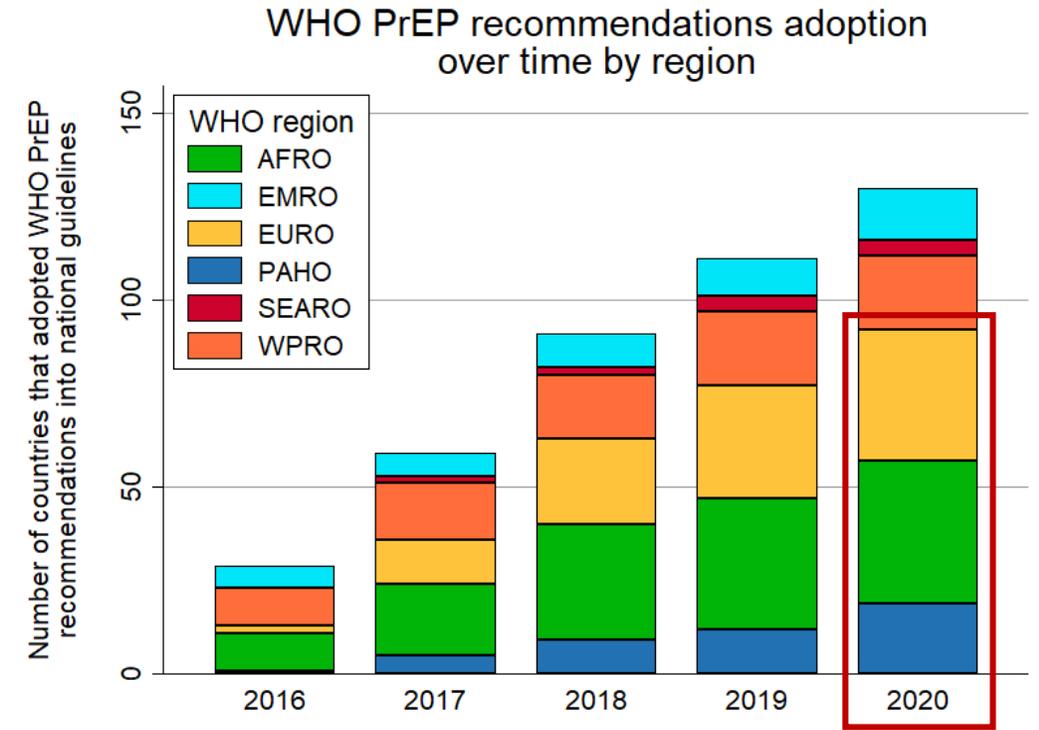
Countries with PrEP in national guidelines

2020 (preliminary data)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO; GAM
Map Production: HQ UCN/HHS/TPP
World Health Organization



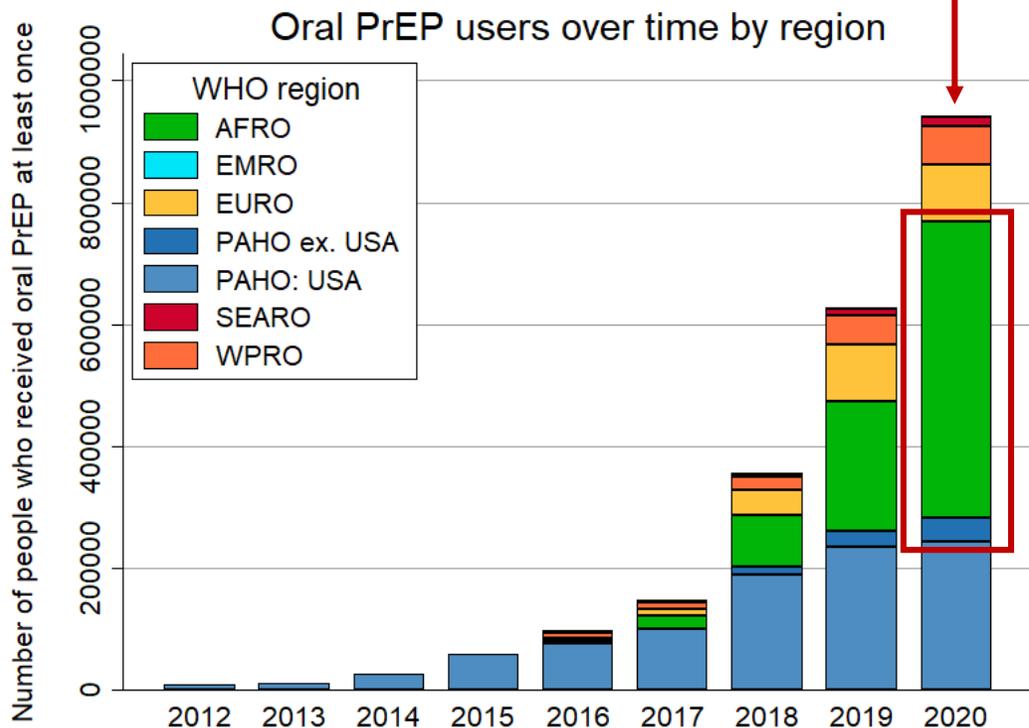
Data source:

WHO reporting; Global AIDS Monitoring.
Data for 2020 are preliminary.

Methods:

Countries were counted as 'adopted' even if guidelines have not yet started implementing PrEP guidelines.

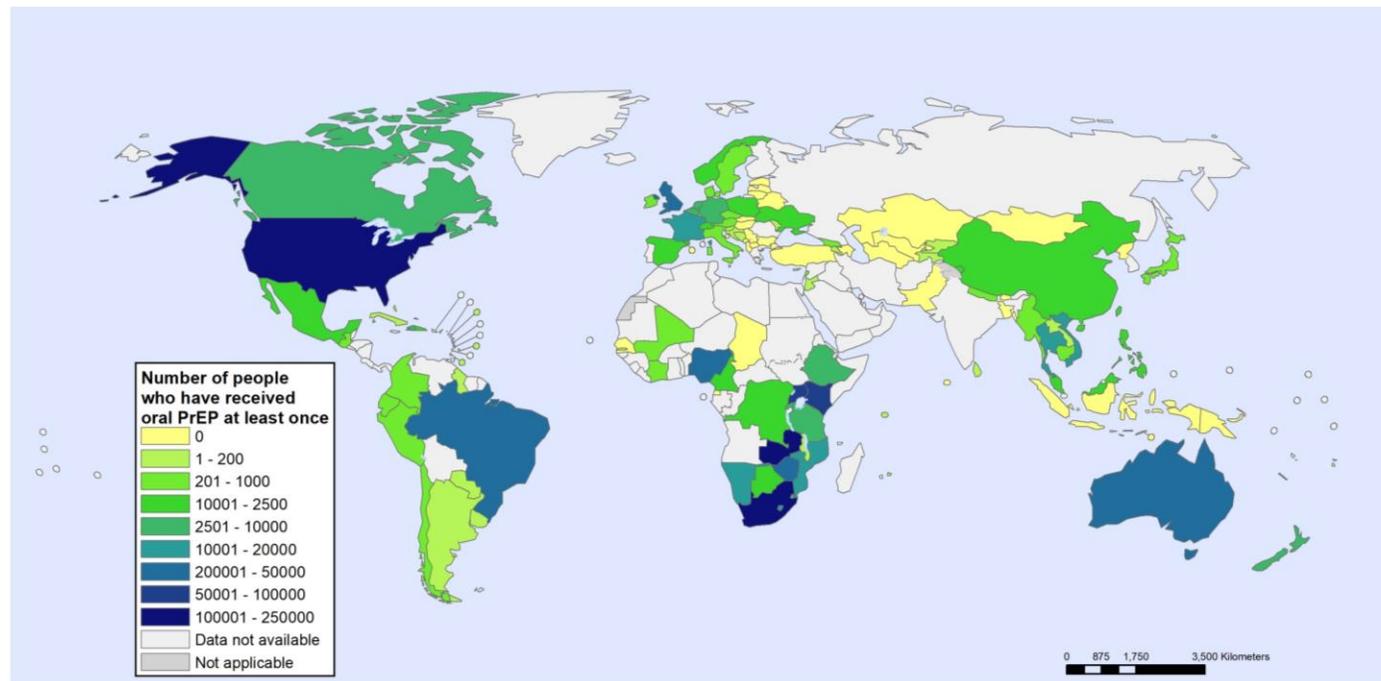
Significant growth in global PrEP use in 2020 despite COVID-19 disruptions → still room for growth and more PrEP options



Global oral PrEP use

(#people received oral PrEP at least once)

2020 (preliminary data)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO; GAM
Map Production: HQ UCN/HHS/TPP
World Health Organization



© WHO 2021. All rights reserved.

Data source:

WHO reporting; Global AIDS Monitoring.
Data for 2020 are preliminary.



WHO's work on dapivirine vaginal ring – started in 2018

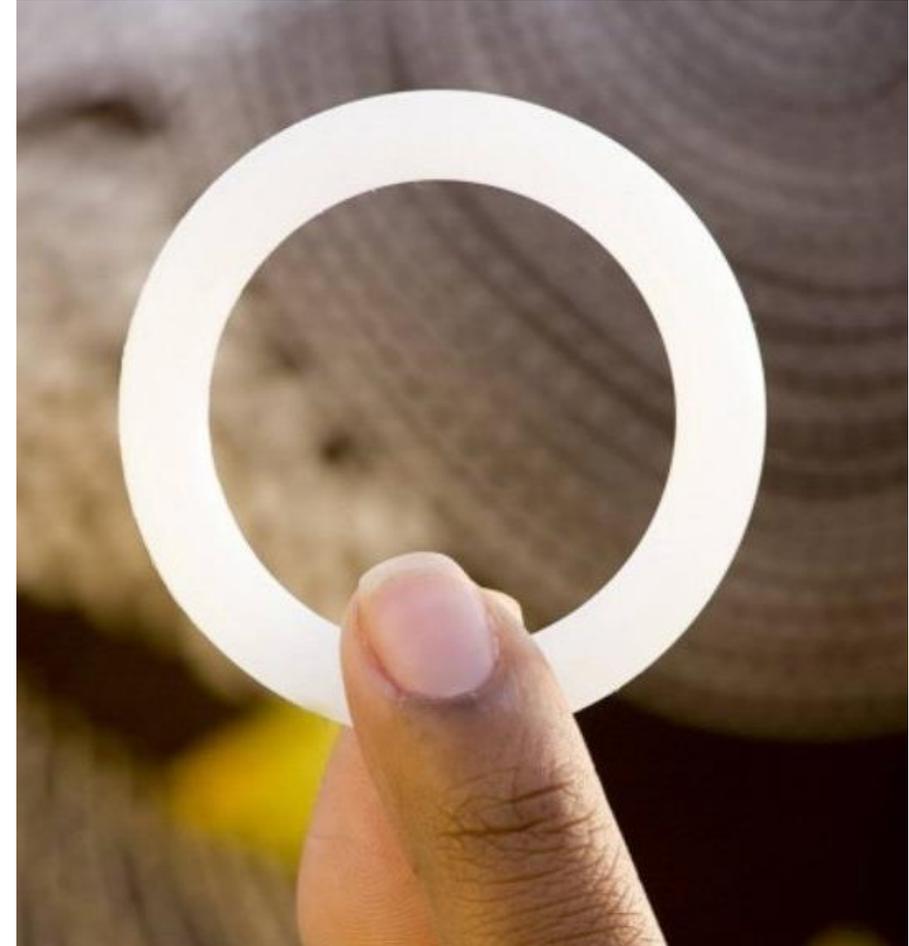
The Dapivirine Vaginal Ring (DPV-VR) is indicated for reducing the risk of HIV-1 infection via vaginal intercourse in sexually active HIV-uninfected women **18 years and older in combination with safer sex practices.**



- WHO recognized the **potential benefit** of additional options, including the **dapivirine vaginal ring (DPV-VR) for PrEP** for women at risk for HIV, particularly in high HIV-incidence and prevalence settings.
- Has public health relevance and **provides individual choice for women.**
- WHO's policy supports **Oral PrEP** provided in the context of HIV combination prevention

DPV-Vaginal Ring Regulatory Story

- **IPM** pursued approvals from global and national regulatory authorities to license the product in countries where women face the highest risk
- Followed **EMA-Article 58 procedure**
- While ongoing data collected from two OLE studies, **DREAM** and **HOPE**, provided the ring to former **Ring Study** and **ASPIRE** participants
- Additional data needed on **safety in pregnancy and breastfeed and adolescents <18 yrs**



DPV-VR Ring Regulatory Story

- WHO convened interval working group to review interim and final data from OLE studies
- WHO convened regulatory meeting with African SRAs to alert them to EMA Article 58 process and the WHO **CRP (Collaborative Regulatory Process) to speed up process**
- During EMA Article 58 process, WHO, with women at risk of HIV, made the case that an additional product would **improve choice** as some women are reluctant to take oral PrEP & have difficulty with continuation
- While contraceptive vaginal rings have been available for several years, the **DPV-VR is the first vaginal HIV prevention product.**
- Research is under way to develop a vaginal ring that includes both **contraception and HIV prevention** & 3-month product

EMA Article 58 – 24 July 2020



- **DPV-VR submitted to EMA under a regulatory procedure (Article 58)**
 - Allows the Agency to assess the quality, safety and efficacy of a medicine and give an opinion on its benefit-risk balance when used in low- and middle-income countries outside the EU.
 - Medicines submitted under this programme are assessed by EMA with WHO and regulators of target countries. These medicines must meet the same standards as those intended for EU citizens.
- **EMA's human medicines committee (CHMP) provided a positive benefit-risk opinion** on the use of the DPV-VR for HIV prevention on 24 July 2020
 - **Reducing the risk of HIV-1 infection via vaginal intercourse in HIV-uninfected women 18 years and older in combination with safer sex practices when oral PrEP is not/cannot be used or is not available**
https://www.ema.europa.eu/en/documents/medicine-outside-eu/dapivirine-vaginal-ring-25-mg-product-information_en.pdf
- CHMP scientific opinion is part of **EMA's cooperation with WHO, named EU-Medicines 4 All (EU-M4all)** under article 58 of Regulation (EC) No 726/2004;
- WHO worked with EMA and patient representatives during the assessment DPV-VR
- CHMP listened directly to the testimony of two women living in endemic countries during the evaluation process.
- **National regulators can use the CHMP's scientific assessment to decide on the use of the medicine in their countries**



WHO Prequalification (PQ)

- **Following the positive scientific opinion from the EMA under Article 58 –**
 - November 2020, DPV-VR was included on the WHO's prequalification (PQ) list of medicines
 - Global Fund placed DPV-VR on preferred drug's list (no guarantee of procurement unless budgeted)
 - PEPFAR preparing to put it on priority commodity list in 2022
 - FDA agreed to review dapivirine ring
 - WHO Essential Medicines List (EML) Review – pending, and
 - WHO HHS Department developed recommendations on its use



DPV-VR Guidelines Process 2020-21



- **More than half of all new HIV infections are among women and girls**
 - Approximately 7,000 young women aged 15–24 years become infected with HIV each week.
- Continued HIV transmission **despite current prevention efforts**, including oral PrEP, and expanding treatment programmes suggests more is needed.
- The DPV-VR is a **female-initiated option** to reduce the risk of HIV infection.
- **To use, the ring**
 - must be worn inside the vagina for 28 days, after which it should be replaced by a new ring.
 - is made of silicone and is easy to bend and insert.
 - works by releasing the ARV drug, dapivirine, from the ring into the vagina slowly over 28 days.

DPV-VR Summary of the evidence

A review and analysis of DPV–VR trials demonstrated that the **ring is effective in reducing the risk of acquiring HIV infection.**

- Two RCTs reported that the DPV–VR was approximately **30% effective in reducing HIV infection** in intention-to-treat analysis.
- Two OLEs found **increased efficacy, increased adherence and increased retention** relative to the randomized controlled trials
 - The results from one of the OLEs indicated a **62% reduction in HIV transmission**, comparing study results to a simulated control
- **No difference** in the treatment and placebo arms **of AEs related to pregnancy, fetal outcomes and/or infant outcomes.**
 - Number of pregnancies was small so ongoing trials are further assessing safety data during pregnancy and breastfeeding
- The dapivirine ring **acts locally, and systemic absorption is low**
- Research on **values and preferences** indicate ring use is considered **highly acceptable**



DPV-VR Recommendation

The dapivirine vaginal ring may be offered as an additional prevention choice for women at substantial risk* of HIV infection as part of combination prevention approaches.

(conditional recommendation; moderate-certainty of evidence)

- Substantial risk of HIV infection is defined as HIV incidence greater than 3 per 100 person–years in the absence of PrEP
- For the recommendation on the dapivirine vaginal ring, the term women applies to cisgender women, meaning women assigned female at birth. There is no research at this time to support the dapivirine vaginal ring for other populations.
- Although the studies reviewed did not directly compare oral PrEP to using the DPV vaginal ring, current evidence suggests that oral daily PrEP, when taken as prescribed, has greater efficacy for HIV prevention than the dapivirine vaginal ring.
- **Oral PrEP should be offered at sites where the DVP ring is provided to enable women to make a choice.** Women should be provided with full information and counselling on the available prevention options and their relative efficacy and safety and counselled to help them to make an informed choice regarding the best option for them.



Implementation considerations / Research gaps

- Addressing the provision of the DPV-VR as part of **comprehensive services**;
- Ensuring women are offered full information in order to make an **informed choice** about the benefits and potential risks when considering to use the ring;
- Careful messaging around '**efficacy**' for providers and users
- **Young women** (and adolescents <18 years when approved in this group, following bringing safety study results) may need more support during initiation and for continuation;
- Acceptability among women from **key population groups**, esp sex workers;
- Additional **adherence support** and **demand creation**;
- **Training and support for providers** to understand and be able to offer this new product;
- Further information on **safety in pregnancy and breastfeeding** and **cost-effectiveness**.



WHO DPV-VR: Country regulatory & Implementation Status

- **DPV-VR submitted for regulatory approval** to the following countries in Q1 2021
 - South Africa (Lesotho & Eswatini approval under South African SRA)
 - Zimbabwe
 - Rwanda
 - Uganda
 - Malawi
 - Tanzania
 - Zambia
 - Kenya
- Eswatini and SA will include **DPV-VR in GF proposals**
- PEPFAR supporting market preparation in their COP 2021; implementation in 2022



Cost of DPV-VR in early adopter countries

- Current costs are **\$9-12 per ring** for procurement depending on volume
- Goal with high volumes that costs will **decrease to \$ 5 per ring** to be competitive with oral PrEP pricing





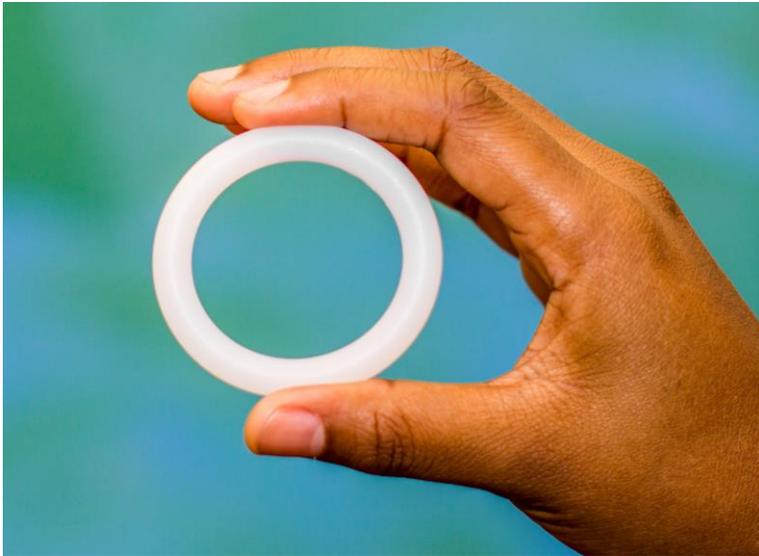
IAS 2021
18 – 21 July

Summary

- **July 2020** - EMA - positive scientific opinion on DPV-VR as an HIV prevention option for women ≥ 18 yo
- **November 2020** – prequalified by WHO
- **January 2021** - WHO recommendation that countries offer the ring as an additional HIV prevention choice for women as part of combination HIV prevention
- **2021** - National medical regulatory authorities: Kenya, Malawi, Rwanda, South Africa, Tanzania, Uganda, US, Zambia and Zimbabwe reviewing the ring for licensure and approval
- Zimbabwe and Zambia- planning rollout & sensitizing HCWs & pilot studies

Notes:

- *Most users will be cisgender women; all studies to date conducted in cisgender women*
- *May be other populations who have receptive vaginal/frontal sex, who may also benefit from using the ring*
- *Needs of other populations should be considered when programs are being developed*





 **IAS 2021**

Acknowledgements

- Rachel Baggaley
- Michelle Rodolph
- Robin Schaefer
- Mathias Stahl
- Women helping WHO with Values and Preferences
- WHO Guidelines Development Group

