Article among sexual exposure, anal sex is the

Articlereviewed: Baeten JM, Palanee-Phillips T, BrownER, et al. Use of a vaginal ring containing dapivirinefor HIV-1 prevention in women.

New England Journal of Medicine. 2016; 375(22): 2121-2132. IntroductionWith 1 million deaths in2016 and 1. 8 million new cases of infection, HIV remains a global healthproblem.

By the end of 2016, more than 35 million people have lost their lives toHIV. African region bears the heaviest burden with 25. 6 million people livingwith HIV in 2016 and two thirds of the global total infection cases1. Sexual and parenteral exposuresmake up the risks of HIV acquisition. Among sexual exposure, anal sex is the riskiestof contracting HIV infection followed by heterosexualvaginal sexual intercourse. For parenteral exposure, blood transfusion and contaminatedneedles sharing are riskiest non-sexual exposures for HIV infection2.

Although the use of condom and ARThas reduced the risk of HIV with sexual intercourse3, the overall HIV pandemic is still worrying because fundamentalbehavioural changes in preventing HIV such as traditional abstinence, loyaltyto a single partner, to the use ofcondoms are not always practised. Emergence of PrEPHighly active antiretroviral therapy (ART) has played a vital role in decreasing HIV related mortality, lowering viral load in the the spread of the disease. New HIV infections fellby 39% between 2000 to 2016 due to the introductionof ART, and it is estimated that morethan 13 million lives have been saved1. Given all efforts in creating a HIV vaccine have failed miserably, pre-exposureprophylaxis(PrEP) – the use of oral and topical use of ART is therefore deemedthe most promising and effective

methods for HIV prevention4, apart from condoms andmale circumcision. To stop the global onslaught of HIV, WHO stronglyrecommends initiation of ART in the entire HIV population to reducetransmission and recommends the use of PrEP as one of the prevention tools forthose who are prone to infection1. Among the newer inventions of HIV prevention, oral PrEP has emerged as one ofthe most effective tools. A combination of tenofovir andemtricitabine (Truvada) has been approvedfor this purpose in many countries.

Although Truvada has 99% protection rate on100% adherence, the protection rate decreases significantlyon non-adherence. If not taken daily, oral PrEP has lower so-called " forgiveness" rate (i. e. theallowance in missed doses) in females as compared to men forgivenesswhich could be due to a lower concentrationof these drugs in the vagina as comparedto male genitals and intestine5. Thus some trials inAfrican women have even failed to show any benefits due to poor adherence6. It is also important to notethat daily oral PrEP may not be an affordableoption in resource-poor countries.

Other concerns with oralPrEP are the risk of development of resistance to antiretroviral drugs; high toxicity related to antiretroviral medications; and concern that people may lose restraintby stop using condoms while on PrEP and thus neutralizing the benefit of oralPrEP7. Consequently, there is an urgent need to find alternative methods of HIV prevention. An ideal solution will be of less toxicity witha lower risk of resistance development, better adherence, and cost-effectiveness. For this purpose, researchersturned their attention to the topical useof antiretroviral drugs.

One of the topicalmedication that has been tested in various trials is 1% topical gelof tenofovir. In CAPRISA study it showed the safety and effectiveness inpreventing new HIV infection in women8. However, it was much less effective when compared to oral PrEP, and hadthe problem of adherence as it was required to beused on a regular basis. Thereforeit did not do well in successive trial8. ASPIRE: a study to understand efficacy of dapivirine vaginal ringKeeping in view thehighest prevalence rate of HIV-1 amongsub-Saharan women, ailing economicsituation, poor adherence to oral PrEP or tenofovir gel, the need was felt for that was effective and easy to use. One option that seems to be morepracticable in sub-Saharan Africa is the use of vaginal rings. There was astudy done by JM Baeten and his team in 2016 to explore the effective andefficacy of such rings.

These rings can be inserted inside the female genitals, containing slow releasing antiretroviral drug. Thus vaginal rings containing Dapivirine (a non-nucleoside HIV-1 reversetranscriptase inhibitor) were developed. These rings can be inserted just oncea month. Moreover, dapivirine rings are cheaper to manufacture, thus making itaffordable and scalable in future usage, especially in the less developedcountries8.

Dapivirinerings provide continuous release of drug to the vaginal mucosa, and its deployment is not dependent on the coitalactivity. Further, vaginal rings are easierto store, transport, and have fewerrequirements for supply chain, making them a better fit over once a day topicalgel for use in developing countriessettings9. In phase I and II clinical trials, they were found to be safe for use. With vaginalrings, plasma level of Dapivirine is 1000 times less in comparison tothe oral dose.

Thus finally in August2002, phase III study of these vaginal rings was initiated to find out theeffectiveness of these rings in a much moresubstantial population group. There is an important reason for choosing the sub-Saharanregion. For the treatment studies, onehas to find the people who are infectedwith HIV-1. But for preventive studies, areas with high incidence and prevalence arerequired, as preventive measures used insuch region would provide more accurateand productive data. The region with higher prevalence also requires smaller sample size, meaning participants.

Women in the sub-Saharan region are atapproximately 5% risk of contracting HIV-1 infection in the period of one year, which is highest in the world. It was a three-year studythat was carried out between August 2012 to June 2015. Participants of thestudy were sexually active, non-pregnant, non-HIV positive women from Zimbabwe, Uganda, Malawi and South Africa. It was a multi-center study (15 sites) thatenrolled women aged 18 to 45 years of age. The primaryaim of the study was to find out the effectiveness and safety ofdapivirine vaginal ring in comparison to placebo, in HIV prevention. Thesevaginal rings need to be replaced just once every four weeks. Rings give womencontrol over their health, and once a month means that compliance would be lessof a problem, not to mention the lower cost and toxicity.

In the study, all femaleparticipants were randomly divided into two groups, one group was given 25 mgdapivirine vaginal rings while another groupwas given similar looking silicon rings(placebo). They were provided education on using the rings, and they have tocome to the clinic once a month forfollow-

up investigations and to receive the newer ring. Researchers knew fromexperience that adherence is a big problem in sub-Saharan Africa.

Providing education and rings towomen does not necessarily improve it. Thus on a quarterly basis plasma samples were collected and measured toconfirm that ring was used for a whole monthand was not inserted just before the visit to the clinic. Women were given thenext ring only when they returned the used one to the clinic.

After a year of the trial, used rings were analyzed againstthe objective assessment of adherence – remaining amount of dapivirine in themto be less than 23. 5mg (with at least 1. 5mg released). The trial was designed to achieve60% lower HIV-1 infection rate in those using dapivirine vaginal rings ascompared to placebo, with a confidence levelof 90%.

Assuming the annual prevalence rate of5% in placebo group (based on earlier trials), it was calculated that at least 120 HIV-1acquisition events among 2600 participants would be required for the clinical trial to be successful. This study enrolled 2629 women. In the study 2614 women completed at least onefollow-up test for HIV-1 infection, resulting in accumulation of total 4280human years of follow-up.

Mean follow-upin the trial was for 1. 6 years, and 1024participants were followed up for more than twoyears. In the dapivirine group, drug was detected in plasma in acceptable level in 82% of cases, and in 84%cases, the returned rings had dapivirine less than 23. 5mg (meaning that they were used by theparticipants). At the end of the trial, 168 of the 2629 participants testedpositive for the HIV-1 virus. 97 testedpositive in the placebo group and

71 in the dapivirinegroup, it means that incidence of HIV-1 in dapivirine groups was 27% less thanin placebo. In the following analysis, data from the two sites were excluded due to poor adherence andfollow-up, and the analysis demonstratedthat HIV-1 was in fact 37% less in the dapivirinegroup.

In the trial, it was also noted that dapivirine rings had no effect in those below the age of 21 dueto poor adherence and other behaviour issues. Thus when the data was analyzed for participants of about 25 yearsof age, it was found that HIV-1 prevalence was 61% less in the dapivirine group as compared to those onplacebo. Although the trial failed to meet the overall expectations (demonstratingjust 27-37% fewer incidences against thetarget of 60%), it is quite clear that results were significant. The more in-depth analysis shows if not due to somefactors, results would have been much higher and would have been above the targeted 60% protectionrate.

There are several reasons for the lower protection rate in thetrial. Firstly, there was very poor adherence in those younger than 21, andeven in those of 25 or below. Secondly, real adherence in those above 25 could also be lesser as the plasma analysis oranalysis of vaginal rings do not prove that these rings were used during the whole period. Thirdly, we see that in factonly half of the participants continued to be part of the trial after two years. Another reason for low results was that genital tract of those below 21 yearsis more susceptible to HIV-1 infection10. Asubsequent study demonstrates that higher adherence might provide HIV-1protection rate of greater than 65% by analysing on the returned rings withresidual Dapivirine ? 22mg compared to ASPIRE level ? 23.

5mg11. This resultexceeds the 60% target protection rate and demonstrates the efficacy of thering in preventing HIV-1 infection and gives confidence for future studies tofurther explore its usage. Study LimitationsWhen we look carefully atthe methodology of the trial, somedeficiencies are quite visible. Firstly, the trialhas undoubtedly failed to motivate the participants to take part in the studyand convey the expected benefits to them. Thus due to the fears of side effectsor inadequate understanding; few participants continued to use those rings forthe whole period of the clinical trial (mean follow-up period of 1.

6 years, against the targeted three years). Another deficiency is thatthe methodology of accessing adherence. In the trial, quarterly plasma levels of dapivirine were checked to see if participants wereusing the rings or not, but positive plasma levels can be achieved by merely inserting the ring about eight hoursbefore giving the blood for the test.

Thus it is entirely possible that many ofthem were not using the rings all the time. Instead, they just inserted the ring a day before the visit to theclinic. Using the vaginal ring to preventHIV-1 infection was evidently a new thingfor the participants, it is quitepossible that many of them were just notcomfortable in integrating the vaginal rings into their lives. Furthermore, the trial didnot account for anal sex during the study period. Anal sex is often associated with high transmissionrates. Vaginal rings would not be protective in such case and participants wereonly asked about anal sex at the beginning of the trial retrospectively but notduring the trial. Thus for variousreasons, it seems highly possible that it may have distorted the result.

Moreover, the result ofthe per protocol analysis – assessing the results of those who stuck toprotocol (meeting the adherence standards) is 37%, compared tointention-to-treat analysis of 27% (analyzing all randomized women), suggestingthat non-adherence is an important factor. Given the fact that the trialresearchers have admitted that the non-adherence threshold was set too low12(i. e. easy to be non-adherent) – with two sites being excluded from the perprotocol analysis – it potentially distorts the per protocol analysis and underminesthe concluded efficacy (biological effect of the treatment) of theintervention. In addition, it is quite possible that the male partners of manyof the participants had a negative influenceon them. Although dapivirine rings arefor females, but this does not mean thattheir sexual partners have no part to play in it.

It is entirelypossible that male partners of some of them were cynical or even worried about the use of such thing as a vaginal ring, for reasons of poor literacy, superstition, or other culturalreasons. During the trial, the rate ofusage of condoms by male partners was not takeninto consideration, though it is possible that due to increased HIV awareness orfear of other diseases caused by the participation of their female partners inthe trial may have led to the more frequent use of condoms by the men. Finally, it should be noticed that trial was done in the black women of the sub-Saharanregion. It is not a multi-ethnic trial. African women are known to bemore predisposed to HIV infection due to genetics, higher prevalence ofvaginosis, and dysbacteriosis.

Lactobacillus has a protective role inHIV, but a higher incidence of vaginal dysbacteriosis in the sub-Saharan regions wouldalter the effectiveness of

topical prophylaxis13. These several deficienciesin the trial maychange the results in both ways, eitherfalsely showing higher protective rate or a lower one. These shortcomings are to be rectified in the future studies. Considering thatdapivirine vaginal ring decreased the incidence of HIV-1 more than 50% in theage group above 21, there is real needfor more clinical trials.

We mustunderstand that initial trials with oralPrEP were also poor due to low adherence. Most of the trials with oral PrEP drugsshowed far better results when they were carried on as open-label trials with afocus on compliance14. Thus the ongoing open-labeltrials on dapivirine vaginal rings (e. g. DREAM, HOPE and MTN-036)15, 16 are expected to delivermore reliable and stronger evidence for the effectiveness and efficacy of therings with better education and control on adherence.

Such study design canhopefully improve the non-adherent situation for all females, including the agegroup from 18-21 that ASPIRE failed to address. ConclusionIn conclusion, it must be understood that African females are bearingthe highest burden of HIV-1 epidemic, inthe most prominent areas of the highest proportion of HIV new infection in theworld17 despite efforts like sexual education, counseling, providing free condoms. Earlierstudies also demonstrated problem in sub-Saharan Africa. The dapivirine vaginal ring has shown itssafety and efficacy. It is less toxic than oral drugs, more importantly, it is much easier to use, meaningadherence would be less of a problem. Studies have indicated that those whoused it found easier to adhere andintegrate vaginal ring into their day to day life, especially with the progressof time18. Such vaginal ring would also be cost effective. Hencethe ongoing second phase III trials would be of great importance.

Way before ASPIRE, dapivirine was tested on vaginal rings incombination with maraviroc (an entry inhibitor) in 2009, which showedlimitations in its efficacy (as a combined effect). Top priority had therefore beengiven to dapivirine alone in research efforts, until now19. Focused research effort canexpedite the research on dapivirine, helping us understand its role andeffectiveness as a topical antiretroviral agents in HIV-1 prevention. Hopefully, thisantiretroviral ring can give us an answer to our current calling for HIV-1prevention. It seems to give hope as a second tool for prevention (after PrEP)which can be used under a woman’stotal control – being able to be kept secretly from men, which makes it extremelybeneficial, especially for females who are unable to get their partners toconsent to mutual monogamy or condom use.