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Residual hormone levels in used contraceptive rings as a measurement of adherence to vaginal ring use

Richard E. Haaland[a,*], **Angela Holder**[a], **Tammy Evans-Strickfaden**[a], **Beatrice Nyagol**[b], **Mumbi Makanga**[b], **Boaz Oyaro**[b], **Felix Humwa**[b], **Tiffany Williams**[c], **Eleanor McLellan-Lemal**[a], **Mitesh Desai**[a], and **Michael J. Huey**[d]

[a]Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, GA, USA 30329

[b]KEMRI/CDC Research Field Station, P.O. Box 1578, Kisumu, Kenya

[c]ICF International, Assigned to Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA 30329

[d]Emory University Student Health Services, Emory University School of Medicine, 1525 Clifton Road, Atlanta, GA, USA 30322

Abstract

Objective—This study sought to measure residual contraceptive hormone levels in vaginal rings as an adherence marker for monitoring product use in clinical trials.

Study design—Residual etonogestrel and ethinyl estradiol levels from used NuvaRings® of 26 self-reported adherent women enrolled in a clinical trial of vaginal ring acceptability were compared to those from 16 women who used NuvaRing® as their contraceptive choice.

Results—Twenty-one (81%) clinical trial rings had contraceptive hormone levels within the range of those used as a contraceptive choice. Five returned rings had unused or discordant levels of residual contraceptive hormones.

Conclusion—Residual vaginal ring drug levels could help assess adherence in clinical trials.

Keywords

Vaginal ring; Adherence; Contraception; Multipurpose technology; HIV

1. Introduction

Prevention of HIV sexual transmission through antiretroviral (ARV) drugs as preexposure prophylaxis (PrEP) can be highly effective when individuals adhere to prescribed ARV regimens [1]. Measuring adherence to PrEP regimens has relied primarily on participant

*Corresponding author. Tel.: +1 404 639 4817; fax: +1 404 639 2736.

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self-report that can be unreliable (e.g., overreporting, recall issues, social desirability) or blood ARV concentrations that may not provide accurate measures of cumulative drug exposure over extended periods of use [2]. HIV PrEP interventions currently in development include multipurpose vaginal rings containing ARVs to prevent sexual transmission of HIV in addition to hormonal contraceptives to prevent pregnancy [3]. New analytical approaches to assess adherence to multipurpose vaginal rings are needed to better evaluate the safety and efficacy of these new intervention strategies [2,4,5]. Residual levels of the ARV dapivirine in used vaginal rings have recently been used to inform measures of adherence and efficacy for vaginal rings in clinical trials for HIV prevention [5,6]. Our study sought to determine if residual synthetic hormone levels in used contraceptive vaginal rings could provide an objective measure of vaginal ring use during a clinical trial.

2. Materials and methods

Sixteen NuvaRings® were collected following 21 days of self-reported use from female volunteers using NuvaRing® as their method for contraception at the Emory University Student Health and Counseling Services in Atlanta, GA. Another 26 NuvaRings® were collected from women in Kisumu, Kenya, who self-reported complete adherence to the prescribed 21 days of NuvaRing® use during the first month of a clinical trial of acceptability, adherence and biologic effects of a contraceptive vaginal ring. NuvaRings® in sealed packaging from the manufacturer were considered to be unused rings for comparison. We extracted residual etonogestrel and ethinyl estradiol from NuvaRings® using ethyl acetate and measured synthetic hormones using high-performance liquid chromatography as previously described (Supplementary Methods) [7]. Used and unused rings were extracted and measured in parallel to calculate the amount of residual etonogestrel and ethinyl estradiol in the used rings as a percentage of that measured in unused rings. We considered used rings with residual etonogestrel and ethinyl estradiol levels greater than 95% of those measured in unused rings to be indistinguishable from unused rings (Supplementary Methods).

3. Results

The 16 vaginal rings from United-States-based female volunteers using NuvaRing® as their chosen contraceptive method had relatively narrow ranges of residual etonogestrel (mean 75% of unused rings; range 70%–79%) and ethinyl estradiol (mean 86% of unused rings, range 80%–91%; Fig. 1). Three volunteers reported removing the vaginal ring for less than 1 day during the prescribed 21 days of use, but the residual synthetic hormone levels in these used rings were indistinguishable from the other 13 rings from this group (Fig. 1). Based on the values from these 16 vaginal rings, we established adherent NuvaRing® use ranges (mean ± 2 standard deviations) for residual etonogestrel (69%–81%) and ethinyl estradiol (79%–93%) to evaluate vaginal rings collected during the Kenya clinical trial of NuvaRing®.

Twenty-one (81%) of 26 vaginal rings from Kenyan participants had both residual etonogestrel and ethinyl estradiol values within the adherent ranges derived from current users in the United States (Fig. 1, Table 1). Three (12%) vaginal rings had residual etonogestrel and ethinyl estradiol levels indistinguishable from those in unused NuvaRings®

(Fig. 1, Table 1). Discordant results between residual etonogestrel and ethinyl estradiol levels were obtained for one vaginal ring (Table 1). One vaginal ring contained residual ethinyl estradiol consistent with adherent use but residual etonogestrel (88%) greater than levels consistent with adherent use yet less than levels in unused rings (Table 1). To see if unused or discordant contraceptive hormone results may have been influenced by intravaginal factors, we compared the distribution of diagnosed bacterial vaginosis (BV) among the adherent and discordant groupings. BV diagnosis was not available from current users in the United States but was diagnosed in eight Kenyan participants based on Nugent score: five with adherent contraceptive hormone levels, two with levels indistinguishable from unused NuvaRings® and one with discordant levels (Fig. 1).

4. Discussion

Analytical measures of product adherence such as hormone concentrations in blood are invasive, costly and unable to indicate cumulative product use. As safety and efficacy evaluations of multipurpose vaginal rings begin, new analytical approaches for assessing adherence to these interventions are needed to accurately measure cumulative usage over extended periods of prescribed use. In this study, we measured residual contraceptive hormones to provide an analytical measure of vaginal ring adherence during a clinical trial among a population of women for whom contraceptive vaginal rings are not currently available. Many returned NuvaRings® (81%) from Kenyan clinical trial participants contained residual contraceptive hormone levels consistent with adherent use as determined by current NuvaRing® users, suggesting that residual compounds can provide a measure of vaginal ring adherence. Measuring two contraceptive hormones produced concordant results in 92% of returned vaginal rings, increasing confidence in our assessment of adherence for these vaginal rings. It is not known if discordant residual levels in vaginal rings resulted from unreported vaginal ring manipulations such as usage patterns, from storage conditions or from intravaginal factors affecting atypical contraceptive hormone release. It is unclear how best to interpret the result of 81%–95% residual etonogestrel as it may be an indication of partial use or biological factors affecting contraceptive hormone release. While contraceptive vaginal rings are not currently licensed for use in Kenya, our results suggest that Kenyan women seeking contraception are likely to use vaginal rings as prescribed for at least 1 month; however, previous studies suggest that adherence to vaginal rings can decline over time [8,9]. Longitudinal analysis of used vaginal rings from clinical trial participants will provide better insight into long-term acceptability among women not accustomed to using vaginal rings.

Evaluation of vaginal ring use among clinical trial participants in this study is limited by reliance on self-reported use by current NuvaRing® users in the United States for establishing residual contraceptive hormone adherence ranges. Careful selection of appropriate population-based controls is essential to accurately define vaginal ring adherence in clinical studies. Additionally, variability among biological factors such as vaginal pH, mucus, microflora or STIs may influence release rates of compounds from vaginal rings, and the prevalence of these factors can differ between populations [10]. Our preliminary evaluation of BV distribution with vaginal ring residual outcomes did not reveal

an observable effect of BV on contraceptive hormone release that may affect adherence measures, but should be done with a larger sample size.

Multipurpose vaginal rings and new contraceptive vaginal rings in development are building upon existing technology used in NuvaRing® to improve and control compound release [3]. While the methodology may need to be amended to fit each new product, the testing approach presented here provides a basis for applying new analytical measures of vaginal ring adherence applicable to multipurpose vaginal rings and new contraceptive vaginal rings. Studies that merge analytical outcomes such as residual contraceptive hormone levels with behavioral measures will provide a more accurate assessment of vaginal ring safety and efficacy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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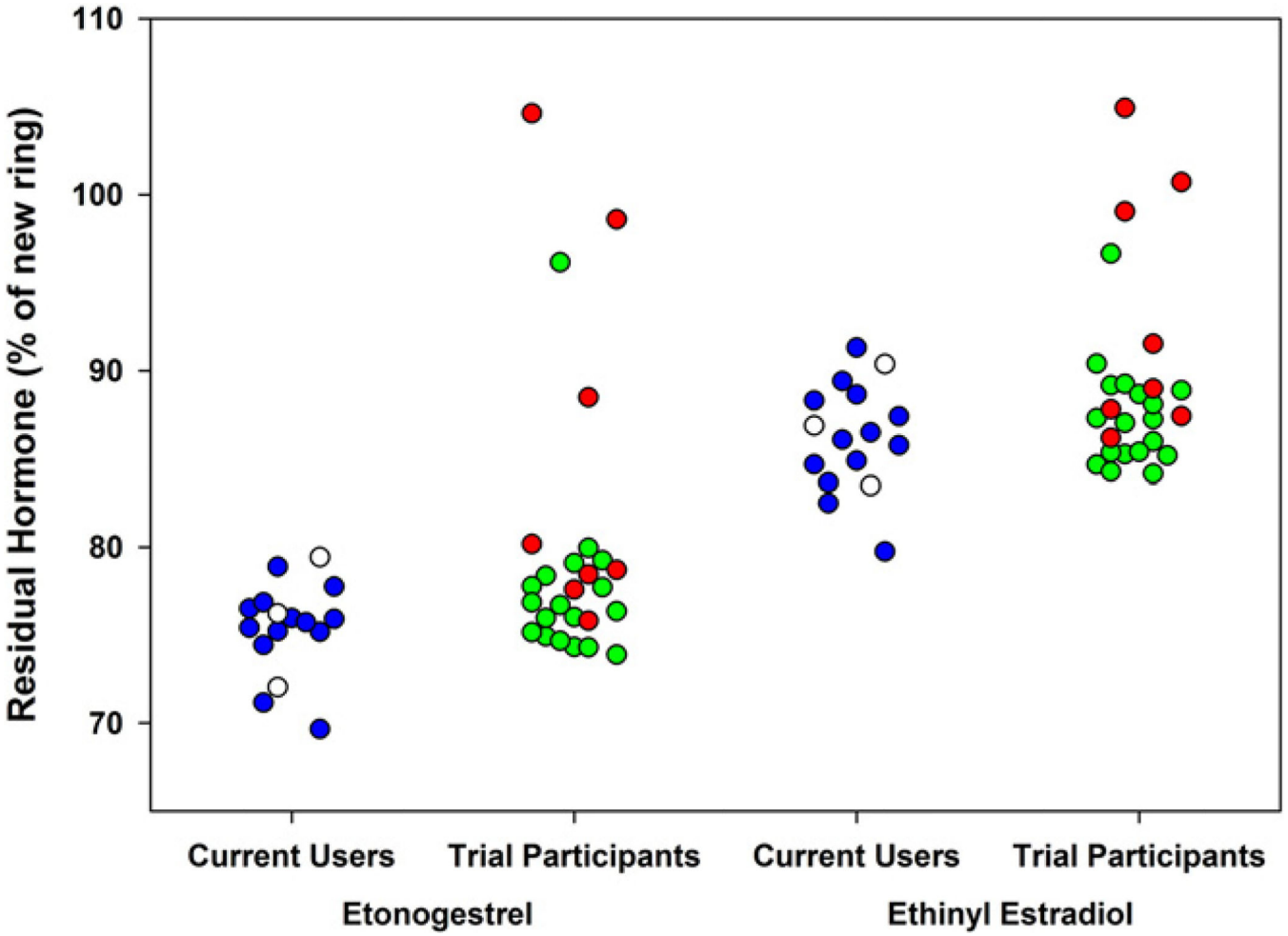

Fig. 1.

Residual etonogestrel and ethinyl estradiol measured in NuvaRings® collected from current users and clinical trial participants following 1 month of self-reported use. Residual etonogestrel and ethinyl estradiol were calculated as a percentage of those measured in unused NuvaRings®. Blue circles and green circles indicate current NuvaRing® users and Kenyan clinical trial participants, respectively. Unfilled circles (n=3) indicate current users who reported removal of NuvaRing® during prescribed use. Red circles (n=8) indicate clinical trial participants diagnosed with BV.

Table 1

Comparison of residual etonogestrel and ethinyl estradiol measured in NuvaRings collected from clinical trial participants (2014–2015)

Etonogestrel[a]	Ethinyl estradiol[b]	Trial participants (*n*=26)
+	+	21
−	−	3
+/−	+	1
+	−	1

[a] Residual etonogestrel <81% (+), >96% (−) and between 81% and 96% (+/−).

[b] Residual ethinyl estradiol <93% (+) and >95% (−).