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Update on the Impact of Depot Medroxyprogesterone Acetate on Vaginal Mucosal Endpoints and Relevance to Sexually Transmitted Infections

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Abstract

Purpose of Review The long-acting reversible intramuscularly-injected contraceptive depot medroxyprogesterone acetate (DMPA-IM) is widely used by cisgender women in Africa. Although DMPA-IM provides reliable contraception, potential effects on the female genital tract (FGT) mucosa have raised concern, including risk of HIV infection. This review summarises and compares evidence from observational cohort studies and the randomised Evidence for Contraceptive Options in HIV Outcomes (ECHO) Trial.

Recent Findings Although previous observational studies found women using DMPA-IM had higher abundance of bacterial vaginosis (BV)-associated bacteria, increased inflammation, increased cervicovaginal HIV target cell density, and epithelial barrier damage, sub-studies of the ECHO Trial found no adverse changes in vaginal microbiome, inflammation, proteome, transcriptome, and risk of viral and bacterial STIs, other than an increase in Th17-like cells.

Summary Randomised data suggest that DMPA-IM use does not adversely change mucosal endpoints associated with acquisition of infections. These findings support the safe use of DMPA-IM in women at high risk of acquiring STIs, including HIV.

Keywords Depot medroxyprogesterone acetate · Vaginal microbiome · Inflammation · Immune cells · Epithelial barrier · ECHO Trial

Introduction

Identifying safe hormonal contraceptive options is an important public health priority, particularly for cis-women in Sub-Saharan Africa, as they are at high risk of both vaginal infections and unintended pregnancies. Uptake of the long-acting reversible intramuscularly injected contraceptive depot medroxyprogesterone acetate (DMPA-IM) has increased over the past decades [1] and is currently the most common contraceptive used in Sub-Saharan Africa [2].

Systematic reviews and meta-analyses synthesising results from >30 observational studies concluded that there was epidemiological, clinical, and laboratory evidence that DMPA-IM use was associated with 40–50% increased risk of HIV acquisition, although findings from observational studies had been inconsistent and likely biased by sexual behaviour [3–6]. In order to address some of the biases and to attempt to assess causality, the open-label Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial randomised approximately 7800 contraceptive-seeking women in a multicentre, open-label trial across 12 research sites in eSwatini, Kenya, South Africa, and Zambia in a 1:1:1 ratio to DMPA-IM, a copper intrauterine device (IUD) or levonorgestrel (LNG) subdermal implant, all of which are highly effective, reversible, long-acting contraceptives [7]. The study did not find a substantial difference in HIV risk amongst the methods evaluated, being powered to detect a 50% increase in HIV incidence across study arms [7]. The HIV incidence was 4.19 per 100 woman-years [3.54–4.94] in the DMPA-IM group, 3.94 per 100 woman-years [3.31–4.66] in the Cu-IUD group, and 3.31 per 100 woman-years [2.74–3.98] in the implant group. In a modified intention-to-treat analysis, the hazard ratios (HRs) for HIV acquisition were 1.04 (96% CI 0.82–1·33, p=0.72) for DMPA-IM compared with Cu-IUD users, and 1.23

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(0.95–1.59, p=0.097) for DMPA-IM compared with LNG implant users [7]. An updated systematic review concluded that the additional HIV incidence data from the randomised ECHO Trial does not support previous concerns that DMPA-IM use increases the risk of HIV acquisition [8••]. Given the outcome of the ECHO trial, the WHO updated their guidance on contraceptive use and recommended no restriction on use of any reversible hormonal contraceptive method for women at high risk of HIV acquisition.

Like previous reports on associations between DMPA-IM use and HIV risk, observational studies have provided conflicting evidence about the relationship between DMPA-IM use and genital mucosal factors associated with HIV acquisition. Thus, sub-studies of the ECHO Trial have evaluated these mucosal endpoints, including the vaginal microbiome, cervicovaginal inflammation, immune cell populations, proteome, epithelial barrier function, and sexually transmitted infection (STI) acquisition risk [9••, 1410••, 11••, 12••, 13••,]. Here, we summarise recent observational and randomised data to provide an update on the effect of DMPA-IM on vaginal mucosal endpoints relevant to risk of acquiring genital infections.

Mucosal Endpoints Associated with HIV Acquisition

Vaginal Microbiome Bacterial vaginosis (BV) is a common dysbiosis of the vaginal microbiome of women of reproductive age, identified using Amsel criteria (that evaluates a clinical array of diagnostic criteria) or Nugent Scoring (which captures bacterial morphotypes on Gram stain) [15]. BV defined by these algorithms often overlaps with a lower female genital tract (FGT) microbiota defined by higher bacterial diversity using molecular sequencing, depleted levels of beneficial *Lactobacillus* spp., and higher abundances of anaerobic species, including *Gardnerella vaginalis*, *Fannyhessea vaginae* (previously *Atopobium vaginae*), and *Prevotella bivia* [15]. Large cohort studies and meta-analyses have consistently found associations between BV (diagnosed by Amsel criteria or Nugent scoring) and increased risk of HIV acquisition [16, 17]. Using 16S rRNA gene sequencing, women with specific bacterial community state types (CSTs), particularly CST-IV (highly diverse, dominated by a range of facultative and/or obligate anaerobes and lack of *Lactobacillus* spp.), are at an increased risk of HIV acquisition [18]. A higher relative abundance of specific bacterial taxa has also been associated with HIV acquisition, including *Prevotella melaninogenica*, *Prevotella bivia*, *Prevotella ihumii*, *Veillonella montpellierensis*, *Mycoplasma* spp., *Sneathia sanguinegens*, and TM7-H1 [13••, 18]. In contrast to relative abundance data, which can vary significantly amongst women based on their microbiota composition and presence of specific taxa, quantitative PCR (qPCR) allows the assessment of absolute concentrations of bacterial species. McClelland et al. found that absolute concentrations of *Parvimonas* species types 1 and 2, *Gemella asaccharolytica*, *Mycoplasma hominis*, *Leptotrichia/Sneathia*, *Eggerthella* species type 1, and *Megasphaera* were associated with HIV risk, in a concentration-dependant manner [19]. Thus, while clinical and molecular methods generally overlap in their description of associations between BV and HIV risk, molecular studies have disagreed with one another on the exact composition of BV-associated bacteria that predict the strongest risk, which is likely partly explained by the differences in the molecular and computational methods applied in molecular analyses.

Several observational studies have suggested that DMPA-IM users are at lower risk of developing BV (by Nugent scoring or Amsel criteria) compared to women not using any hormonal contraceptives [20–25]. In agreement, increases in *Lactobacillus* species or reductions in BV-associated bacteria have been reported in some longitudinal studies that have measured microbiota fluctuations (assessed by qPCR and bacterial culture) before and after DMPA-IM initiation [26–29]. In contrast, others found no change in the absolute concentrations of the BV-associated species *G. vaginalis* and *F. vaginae* measured by qPCR after DMPA-IM initiation, despite a significant decrease in Nugent score [30]. These findings suggest a beneficial shift in the vaginal microbiota composition with DMPA-IM use. Similarly, the vaginal microbiotas of DMPA-IM users in the Vaginal Human Microbiome Project were less likely to have vaginal microbiotas dominated by BV-associated bacteria (measured by 16S rRNA gene sequencing) compared to women using barrier contraception, although this was not associated with a concurrent increase in the relative abundance of *Lactobacillus* species [31].

In contrast, other longitudinal studies reported decreases in vaginal *Lactobacillus* species after women initiate DMPA-IM, as measured by absolute concentrations [32], relative abundances [33], or proportion of women with lactobacilli present by culture [34]. DMPA-IM use correlated with an increased diversity of the vaginal microbiota, assessed by 16S rRNA gene sequencing, in a cross-sectional cohort of Kenyan women [35]. This discrepancy in observational studies does not allow for robust conclusions on the effect of DMPA-IM use on the cervicovaginal microbiota, as many of the reported outcomes could be a result of behavioural differences between women choosing DMPA-IM over other or no contraceptive methods. Randomising women to contraceptive methods is the best method we have to attenuate the confounding effect of behaviour (or any other socio-demographic differences between groups), but this is not perfect, as participants are not blinded to their contraceptive arm.

A sub-study of the ECHO Trial conducted by this team specifically assessed the effect of DMPA-IM initiation on the lower FGT microbiota, compared to the LNG-implant and copper IUD. Brown et al. found that overall bacterial diversity did not significantly increase up to 6 months following DMPA-IM initiation compared to baseline [13••]. Instead, women randomised to DMPA-IM regularly transitioned from *L. iners*- (CST-III) to *L. crispatus*- (CST I-B) dominated communities during the first 6 months of use. Total bacterial 16S gene copies increased significantly in women randomised to DMPA-IM, and this increase was predominantly due to an increase in *Lactobacillus* spp. bacterial load [13••]. In another study that randomised 97 Malawian women with or without HIV to DMPA-IM or LNG-implant and followed them over 6 months, no long-term changes in the genital microbiota were observed with DMPA-IM use in women with HIV and without HIV [36]. Overall, these randomised studies suggest that DMPA-IM use is not associated with non-optimal cervicovaginal microbiota composition that previously has been associated with increased risk of HIV acquisition.

Cytokines Inflammatory responses in the FGT are important to fight invading pathogens. However, increases in specific cervicovaginal cytokine concentrations, independent of the cause, have also been associated with increased risk of later HIV acquisition [37–41]. While there is some heterogeneity between studies and populations, higher vaginal fluid interleukin (IL)-1α, IL-1β, and IL-8 concentrations appear to be associated with increased risk of subsequent HIV acquisition in the majority of studies [42].

Several observational cohorts studies that have included Sub-Saharan African women found DMPA-IM use to be associated with changes in cervicovaginal cytokines, with higher IL-1α, IL-1β, macrophage inflammatory proteins (MIP)-1α, MIP-1β, IL-6, IL-8, interferon (IFN) gamma-induced protein 10 (IP-10), RANTES, C-X-C motif chemokine ligand (CXCL)-6, and CXCL-1 [43–46], while other studies, including longitudinal studies analysing the pre- and post-DMPA-IM initiation cytokine levels, have found DMPA-IM to be immunosuppressive, with decreases in IL-1β, IFN-α, IFN-g, IL-6, IL-8, IL-10, IL-12p40, IL-1 receptor antagonist (RA), CXCL-10, monocyte chemotactic protein-1 (MCP-1), granulocyte-colony stimulating factor (G-CSF), and IP-10 [20, 26, 47–53], possibly in a dose-dependent manner [54], and others found no significant differences in cytokine concentrations between DMPA-IM users and those not using any hormonal contraception in a cross-sectional study [55]. Thus, findings of observational studies describing changes in cervicovaginal cytokines and DMPA-IM use were variable.

Cervicovaginal cytokine levels were evaluated in two independent sub-studies that included samples of women from different sites (Cape Town and Johannesburg, South African and Kisumu, Kenya [9••] and Tshwane and eThekwini, South Africa [56••]) of the randomised ECHO Trial [9••, 56••]. Both studies found no significant differences in cytokine levels 1, 3, or 6 months after DMPA-IM initiation compared to pre-DMPA-IM initiation levels. These randomised data support the conclusion that DMPA-IM use is not associated with changes in inflammatory markers relevant to HIV acquisition risk in the lower FGT.

Immune Cell Populations The number, phenotype, and activation status of genital tract immune cells are an important determinant of risk of acquisition [57]. Cervicovaginal-activated CD4 + T cells that express the HIV co-receptor CCR5, particularly Th17 (CCR6 +) cells, are preferential targets for HIV infection and have consequently been used as a proxy measure for HIV acquisition risk [10••, 58, 59].

Association between DMPA-IM use and increased numbers of cervical immune cells, including CD4+ T-cells, and increased expression of the HIV co-receptor CCR5 have been described in some observational studies [20, 53, 60–63], but not others [34, 51, 52]. In the longitudinal ZimCHIC study, DMPA-IM initiation led to minimal reductions in the number of cervical CD4+ T cells and CD11c+ antigen presenting cells [52]. Two recent longitudinal studies found significant increases in the frequencies of cervical T cells expressing CCR5 after DMPA-IM initiation using both flow cytometry and imaging [50, 64]. In a South African cohort, women using long-term injectable progestins including DMPA-IM had higher frequency and density of CCR5+CD4+ cervical T cells, versus women not using contraception, but these differences may at least partially be due to differences in sexual behaviour [55]. Other phenotypic alterations of cervical T cells have been observed amongst DMPA-IM users including increased expression of the activation marker HLA-DR and a decreased frequency of regulatory [51] and central memory T cells [50]. Since all these cells are potential HIV target cells, the observational data regarding the effect of DMPA-IM on HIV target cell availability in the cervix have been unclear.

From this group, which included a subset of South African women enrolled in the ECHO Trial, randomisation to DMPA-IM was associated with higher frequencies of cervical Th17-like cells at 1 month after initiation, including a highly susceptible, activated population co-expressing CD38, CCR5, and α4β7, while overall frequencies of CD4+ T cells remained stable [10••]. After 1 month, women using DMPA-IM had significantly more Th17-like cells than women using the Cu-IUD or LNG-implant. This finding is supported by RNA-Seq data that showed that DMPA-IM enriched for pathways associated with T cell responses, specifically of genes that function in T cell activation, migration, and communication (Gupta

et al., submitted). Interestingly, the increased abundance of Th17-like cells amongst DMPA-IM users in the ECHO Trial coincided with increased expression of mucosal barrier proteins [10••]. Overall, these randomised data suggest that DMPA-IM initiation may cause increases in cervicovaginal activated or CCR5-expressing CD4 + T cells important for HIV acquisition risk, yet the clinical relevance of these findings is unclear as the changes in HIV target cell frequencies and activation could be counteracted by improved barrier function and not result in increased HIV risk.

Epithelial Barrier Function The integrity of the physical barrier of the genital tract is crucial for the defence against HIV and other pathogens. Thinning of the vaginal epithelium or decreased cell adhesion and tight junction proteins leads to a more permeable epithelium and can be used as a measure for epithelial barrier function [65]. Epithelial barrier modulation by DMPA-IM use has been reported using various techniques, including by assessing structure and protein location of biopsies by microscopy or molecular techniques measuring the expression of functional genes or proteins in cross-sectional and prospective studies.

Several cross-sectional studies have identified proteomic indications of vaginal epithelial barrier disruption amongst DMPA-IM users in FGT secretions, including reduced levels of the growth factors G-CSF and M-CSF, which may suggest epithelial damage [45, 49, 66–68]; increased levels of haemoglobin; decreased levels of epithelial repair, maintenance, and structural proteins [69]; and reduced levels of protease inhibition proteins, including matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) [48, 49, 69, 70].

In a non-randomised prospective study before and after 6 weeks of DMPA-IM initiation versus combined oral contraceptive use, whole-genome transcriptome profiling of the ectocervical mucosa demonstrated that DMPA-IM use resulted in downregulation of genes encoding cell junction proteins involved in epithelial integrity and differentiation, but demographics differed significantly between DMPA-IM and oral contraceptive users which may have confounded these results [71]. Similarly, assessment of ectocervical biopsy tissue from women before and 1 month after initiating DMPA-IM revealed that DMPA-IM use resulted in a decreased expression of the cell-cell adhesion molecule desmosomal cadherin desmoglein-1 (DSG1) and significantly increased mucosal tissue permeability [72]. In a cross-sectional study, expression of genes involved with necrosis was increased in cervical transformation zone tissue, while expression of genes involved with cell proliferation was decreased in women using DMPA-IM versus controls not using any hormonal contraceptive [73]. In contrast to these findings, the total thickness of the ectocervical epithelial layer was comparable between women using DMPA-IM and those not using any hormonal contraceptive in a recent cross-sectional study in Kenyan women [74]. The same observations were made for the vaginal epithelium of Brazilian women [75], while in Swedish women, the vaginal epithelial thickness of DMPA-IM users was greater compared to non-hormonal contraceptive users [61]. In longitudinal studies in women from the USA and Dominican Republic, the number of cell layers and density of E-cadherin, a cell adhesion protein, was comparable prior to DMPA-IM initiation and 6 weeks thereafter [20]. Similarly, no significant change in epithelial thickness, number of cell layers, and E-cadherin and ZO-1, another tight junction protein, was observed after 12 weeks of DMPA-IM use in women from the USA [63], nor after 12 months with regard to epithelial cell layer number [34]. These results from observational studies suggest that epithelial thickness is not influenced by DMPA-IM use, while cell-cell adhesion molecules might be adversely affected.

In a sub-study of the ECHO Trial, RNA-Seq of cervical cytobrushes from women randomised to DMPA-IM revealed a significant enrichment of genes regulating tight junctions in epithelial barriers, including several claudins and junctional adhesion molecules at 1 month post DMPA-initiation versus baseline, but not amongst LNG-Implant and Cu-IUD users (Gupta et al., submitted). Consistent with this, DMPA-IM induced Th17 cells which positively correlated with proteins involved in mucosal barrier integrity, including epithelial cell-cell adhesion junction proteins, protease inhibition, actin cytoskeletal components, and cell-matrix adhesion [10••]. These results contrast previous observational studies reporting downregulation of genes involved in epithelial barrier function. The biological implications of these findings with regard to genital mucosal health are yet unclear. As reviewed elsewhere, tight junction proteins are expressed at higher levels following intestinal epithelial barrier damage, to induce tight junction closure during repair of acute injury [76] but whether the same would occur after vaginal epithelium damage needs to be investigated. Thus, whether the increased expression of tight junction proteins is a result of tissue damage repair or improved barrier function in the FGT remains unknown.

Gupta et al. also found that concurrently with the enrichment of genes regulating tight junctions, gene pathways associated with growth and metabolism (e.g. glycolysis, fatty acid, and protein metabolism) were downregulated amongst DMPA-IM users. Glycosylation of cervicovaginal fluid of the vaginal epithelium provides a barrier to infection, and decreased glycosylation of cervicovaginal fluid proteins could lead to decreased barrier protection [77, 78].

In summary, analyses based on protein and gene expression suggest that DMPA-IM use modulates mucosal barrier function, but it is unclear whether DMPA-IM enhances or impairs barrier function. Differences amongst studies could

partially be due to differences in methodological approaches, or could reflect the timing of sampling and thus, the medroxyprogesterone acetate (MPA) concentration. This is supported by findings from the CAPRISA004 study, which showed a dose-dependent effect of DMPA-IM on genital host protein expression [66]. Women with high serum MPA levels had reduced levels of cervicovaginal proteins associated epithelial barrier repair and keratinisation in support of reduced mucosal barrier integrity with DMPA-IM use, while this was not seen for women with lower serum MPA levels [66].

Bacterial, Protozoal, and Viral STIs Including HIV

Infection with bacterial and protozoal STIs (including *Mycoplasma genitalium*, *Neisseria gonorrhoeae*, *Treponema pallidum* (syphilis), *Trichomonas vaginalis*, and *Chlamydia trachomatis*, and viral STIs, including Herpes simplex virus (HSV-2) and human papillomavirus (HPV)) can increase risk of subsequent HIV acquisition [79–81]. While data evaluating the association between DMPA-IM use and incidence of *M. genitalium* are sparse, a recent systematic review and meta-analysis described a reduced incidence of *T. vaginalis* with DMPA-IM use relative to non-hormonal contraceptive users, and inconclusive evidence for *C. trachomatis*, *N. gonorrhoeae*, and *T. pallidum* [82]. A secondary analysis of the randomised ECHO Trial found that DMPA-IM use was associated with a 20% lower risk of *C. trachomatis* infection compared with LNG-implant use and a 30% lower risk of *N. gonorrhoea* infection compared to Cu-IUD use [12••]. *N. gonorrhoea* prevalence was also lower amongst women randomised to DMPA-IM compared to those randomised to LNG-implant, although this was not significant [12••]. These findings, from both observational and interventional studies, suggest that DMPA-IM use is not associated with increased risk of the common bacterial and protozoal STIs *C. trachomatis*, *T. vaginalis*, and *N. gonorrhoea* but more data are needed to make conclusions regarding risk of acquiring *M. genitalium* and *T. pallidum*.

With regard to viral STIs, systematic reviews concluded that the available observational evidence does not support an association between DMPA-IM use and HPV risk [82, 83]. In contrast, two systematic reviews found evidence that DMPA-IM use increases risk of HSV-2 acquisition [82, 83], while there was evidence of a weak protective effect of DMPA-IM use versus Cu-IUD on HSV-2 acquisition in the randomised ECHO Trial [11••]. Given the associations between HSV-2 and subsequent HIV acquisition [11••], the relationship between HSV-2 risk and DMPA-IM use requires further investigation.

Conclusions

Synthesis of data from the more robust and unbiased studies suggests that DMPA-IM use does not result in notable adverse changes of most of the FGT mucosal endpoints that have been associated with HIV acquisition, including the microbiome, inflammatory markers, and common bacterial and viral STIs, or if anything, is associated with protective changes, except for CCR5-expressing Th17-like cells. Increases in Th17 cells were however accompanied by increases in proteins involved in mucosal barrier function. DMPA-IM users experienced increases in gene pathways involved in junctional proteins, highlighting that the mucosal environment needs to be considered holistically when assessing HIV risk. It needs to be acknowledged that, while reported condom use amongst DMPA-IM users was higher compared to the Cu-IUD and LNG-implant users in the ECHO Trial, data from the biomedical ECHO Trial substudies assessing mucosal endpoints associated with HIV risk support the finding that DMPA-IM use is not associated with adverse FGT health. Overall, these new data support the 'safe' use of DMPA-IM in all women, also those at high risk for STIs.

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Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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