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Efficacy of Tenofovir 1% Vaginal Gel in Reducing the Risk of HIV-1 and HSV-2 Infection

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ABSTRACT: Human Immunodeficiency Virus (HIV) is a retrovirus that can result in rare opportunistic infections occurring in humans. The onset of these infections is known as Acquired Immune Deficiency Syndrome (AIDS). Sexual transmission is responsible for the majority of infections, resulting in transmission of HIV due to infected semen or vaginal and cervical secretions containing infected lymphocytes. HIV microbicides are formulations of chemical or biological agents that can be applied to the vagina or rectum with the intention of reducing the acquisition of HIV. Tenofovir is an NRTI that is phosphorylated by adenylate kinase to tenofovir diphosphate, which in turn competes with deoxyadenosine 5’-triphosphate for incorporation into newly synthesized HIV DNA. Once incorporated, tenofovir diphosphate results in chain termination, thus inhibiting viral replication. Tenofovir has been formulated into a range of vaginal formulations, such as rings, tablets gels and films. It has been shown to be safe and effective in numerous animal models, while demonstrating safety and acceptability in numerous human trials. The most encouraging results came from the CAPRISA 004 clinical trial which demonstrated that a 1% Tenofovir vaginal gel reduced HIV infection by approximately 39%.

KEYWORDS: tenofovir, HIV, HSV, microbicide, vaginal gel

INTRODUCTION

HIV and AIDS. Human immunodeficiency virus (HIV) is a retrovirus that can result in rare opportunistic infections occurring in humans. The onset of these infections is known as acquired immunodeficiency syndrome (AIDS). HIV is subdivided into HIV-1 and HIV-2. HIV-2 is largely confined to West African countries, and is extremely rare in Europe, Central or East Africa and North America. While HIV-2 is similar to HIV-1, it has a different sequence of nucleotides in its genome. The major modes of HIV transmission are sexual contact, exposure to infected blood, infected needles and mother-to-child. Sexual transmission is responsible for the majority of infections; HIV is transmitted via infected semen or vaginal and cervical secretions containing infected lymphocytes.

HIV destroys the human immune system by attacking the CD4+ T helper cells, a subgroup of lymphocytes, which are a type of white blood cell that is part of the adaptive immune system. This leaves the body susceptible to opportunistic infections, which leads to the onset of AIDS. HIV consists of a genome containing two identical single strands of RNA along with two molecules of reverse transcriptase that copies RNA into DNA. Two proteins, known as p7 and p9 are also associated with the genome, which is then surrounded by p17 proteins on the outer core and p24 on the inner core. Surrounding these core proteins is an envelope that contains two HIV-specific glycoproteins, gp41 and gp120 (see Fig. 1).

All retroviruses have three common genes, gag, pol and env, which code for the main polyproteins of the virus. These polyproteins, when cleaved by viral protease, result in the production
of the core proteins (p7, p9, p17 and p24), the replication enzymes (reverse transcriptase, protease and integrase) and finally the envelope proteins (gp41 and gp120). HIV contains six unique genes that code for proteins required to regulate the expression of the HIV genome. Two of these genes are tat and rev, which code for a trans-activator protein and a regulator of mRNA transcription, respectively. The tat protein binds to an RNA sequence on the genome known as TAR (trans-activation response element), which results in an increase in the number of RNA transcripts formed. The HIV genome also includes vif, upr, nef and upu genes, which help in the regulation of transcription.

**HIV replication.** The HIV replication cycle begins with attachment of the virus to CD4 receptors on certain cells of the immune system (T helper cells, lymphocytes and macrophages) and glial cells in the brain (see Fig. 2). Viral attachment occurs via the gp120 envelope proteins (there is estimated to be 220 on each virion). Upon attachment gp120 interacts with another protein on the host cell surface, CD26 (not shown in Fig. 2). This interaction results in the exposure of a site on the gp41 viral envelope protein that fuses the viral envelope with the host cell cytoplasmic membrane, resulting in the entry of the virus into the host cell. The viral coat is removed and the single-stranded RNA genome is reverse-transcribed to double-stranded cDNA by the enzyme reverse transcriptase.

This proviral DNA is transported into the host cell nucleus and integrated with the host genome at specific sites along the chromosome, by the viral enzyme integrase. This integrated viral genome is known as a provirus and is transcribed and translated into new viral proteins. If the proviral DNA is activated it can produce new strands of RNA. This RNA either becomes messenger RNA, and is used for the production of viral proteins, or becomes encased within the viral core to become the new virus.

The **gag** gene is transcribed and translated into a polyprotein called p53, which is then cleaved into the core proteins p7, p9, p17 and p24 by the HIV-coded protease. The pol gene is also transcribed, translated and proteolytically cleaved into reverse transcriptase, protease and integrase polypeptides. The last gene to be transcribed and translated into the polyprotein gp160 is the env gene. Then, gp160 is cleaved into the envelope glycoproteins gp120 and gp41, which are incorporated into the host’s cytoplasmic membrane. The viral particles are then assembled and released slowly from the infected host cell by a process known as ‘budding’ (see Fig. 2).

**HIV Microbicides**

HIV microbicides are formulations of chemical or biological agents that can be applied to the vagina or rectum with the intention of reducing the likelihood of acquisition of HIV. An effective microbicide product has the potential to reduce the global HIV infection rate. The ideal vaginal HIV microbicide must have activity against cell-free and cell-associated HIV. It must not cause damage to the tissue or flora of the vagina. It must be retained in the vagina, act locally and retain its activity in the presence of semen and across a broad pH range.

There are various mechanisms by which vaginal HIV microbicides may prevent HIV infection (see Fig. 3): 1) by destroying the virus as soon as it enters the vagina; 2) maintenance of the vaginal flora, which provides a protective vaginal pH; 3) prevention of HIV binding to CD4 receptors; 4) by preventing the HIV replication process; 5) by providing a physical barrier that prevents HIV from entering the vaginal mucosa; and 6) by prevention of sexually transmitted infection (STIs), which may increase the possibility of HIV infection.

**Reverse transcriptase inhibiting HIV microbicides.** Reverse transcriptase inhibitors (RTIs), which inhibit the viral encoded enzyme reverse transcriptase responsible for the conversion of single strand viral RNA into double-stranded DNA, are being evaluated as HIV microbicides. Both nucleotide and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs) are under evaluation. NRTIs inhibit the process of reverse transcriptase by insertion into the propagating viral DNA, thereby inhibiting further synthesis of DNA. NNRTIs inhibit reverse transcriptase by binding directly to the reverse transcriptase enzyme and inhibiting the conversion of viral RNA into viral DNA.

**Tenofovir.** Tenofovir (PMPA) is an NRTI that is phosphorlyated by adenyate kinase to tenofovir diphosphate, which in turn competes with deoxyadenosine 5’-triphosphate for incorporation into newly synthesized DNA. Once incorporated, tenofovir diphosphate results in chain termination, thus inhibiting viral replication. Tenofovir is currently used in anti-retroviral therapy for the treatment of HIV and is marketed under the brand name Truvada, which is a once daily tablet containing 300 mg of tenofovir and 200 mg of emtricitabine. Truvada has been approved by the Food and Drug
Figure 2. HIV replication cycle.

Figure 3. Potential mechanisms of HIV prevention by a microbicide formulation: (1) provision of a physical barrier that prevents HIV from entering the vaginal mucosa, (2) maintenance of the vaginal flora, which provides a protective vaginal pH, (3) prevention of sexually transmitted infections (STI’s) which may increase the possibility of HIV infection, (4) by destroying the virus as soon as it enters the vagina, (5) prevention of HIV binding to CD4 receptors, (6) preventing the HIV replication process ultimately leading to the prevention of HIV uptake by the immune cells (7) (www.empro.org.uk).
Administration (FDA) for use as a pre-exposure prophylaxis strategy against HIV infection. Tenofovir is also marked as Atripla™ (or Viraday™), which is a once daily combination tablet containing emtricitabine, tenofovir and efavirenz designed to increase compliance of antiretroviral therapy by reducing the pill-burden of HIV-positive patients. It has been demonstrated that there is less chance of HIV developing resistance to tenofovir compared to other reverse transcriptase inhibitors.\textsuperscript{24} Tenofovir’s efficacy, long half-life and safety profile make it an ideal candidate for use as an HIV microbicide strategy,\textsuperscript{27} while a study performed in SIV-positive macaques concluded that when they were treated systemically with either 30 mg/Kg or 75 mg/Kg of PMPA the viral load was significantly reduced. However, the viral load increased when the treatment was stopped.\textsuperscript{28} Tenofovir’s potential for use as an HIV microbicide was further corroborated by successful invivo and invivo assessment of a 1% tenofovir gel,\textsuperscript{27} while two macaque studies of tenofovir gels administered vaginally showed 100% and 80% protection.\textsuperscript{29} Tenofovir’s efficacy against viral challenge in animal models has been established using either pre- or post-exposure prophylaxis administration.\textsuperscript{30–32}

Tenofovir has also been shown to be effective against the herpes simplex virus-2 (HSV-2), with studies demonstrating that a tenofovir vaginal gel not only reduces HIV infection but surprisingly also suppresses HSV-2 infection.\textsuperscript{33} However, it has been demonstrated that administering tenofovir orally has no impact on HSV-2 infection.\textsuperscript{34} Andrei et al demonstrated that tenofovir inhibits the replication of HSV in a range of human clinical isolates and decreases HSV replication in human lymphoid and cervicovaginal tissues ex vivo, while delaying HSV-induced lesions and death in topically treated HSV-infected mice. They concluded that tenofovir inhibits HSV-2 DNA-polymerase, but in order to achieve effective drug concentrations it must be administered topically rather than orally.\textsuperscript{35}

**Clinical Studies and Efficacy**

Tenofovir has been comprehensively studied for safety, acceptability and efficacy. Primarily these studies have focused on the drug in an oral dosage form as part of antiretroviral (ARV) therapy and typically in combination with other antiretrovirals. A three-year trial evaluating the safety and efficacy of tenofovir vs. stavudine when taken in combination with lamivudine and efavirenz showed both compounds to be highly effective in ARV-naive patients, though tenofovir was associated with less toxicity than stavudine.\textsuperscript{36} A study examining a three-drug regimen of tenofovir, abacavir and lamivudine in HIV-infected, ARV-naive subjects showed an unacceptably high virologic non-response, leading to the authors’ conclusion that combination therapies should not be given based on presumed efficacy of the individual drugs.\textsuperscript{37} In the CASTLE study, fixed dose tenofovir-emtricitabine was shown to be effective in combination with either atazanavir-ritonavir once daily or lopinavir-ritonavir twice daily.\textsuperscript{38} The STEAL study compared safety and efficacy of once-daily, fixed dose combinations tenofovir-emtricitabine vs. abacavir-lamivudine, finding that both combinations had similar virological efficacy but abacavir-lamivudine was associated with more serious non-AIDS events, such as cardiovascular events.\textsuperscript{39}

A phase 3 trial measured the efficacy of tenofovir-emtricitabine in HIV-1 infected, treatment-naive adults in combinational therapy with either efavirenz or a newer NNRTI, rilpivirine.\textsuperscript{40} The study showed that the combination with rilpivirine had non-inferior efficacy compared to the combination with efavirenz, with higher virological failure but a more favourable safety and tolerability profile. A single dose tablet combining the integrase inhibitor elvitegravir co-formulated with cobicistat, emtricitabine and tenofovir has been trialled,\textsuperscript{41} showing non-inferiority compared to the widely used combination efavirenz-emtricitabine-tenofovir. The new tablet offers the potential for a complete regimen in a single daily dose for initial treatment of HIV-1 infected patients. In protection against mother-to-child transmission, tenofovir-emtricitabine was trialled in combination with intra-partum and neonatal single-dose nevirapine and was shown to reduce viral resistance to NNRTIs at 2 and 6 weeks after ingestion.\textsuperscript{42} A pharmacokinetic study involving oral tenofovir in combination with atazanavir-ritonavir in heavily pre-treated HIV infected patients suggested the existence of significant interaction between atazanavir-ritonavir and tenofovir.\textsuperscript{43}

The use of these same tenofovir-based oral dosage forms is now being examined in a number of trials to measure the effectiveness of such combinations as a prevention strategy in HIV-uninfected persons to reduce the transmission of HIV. The results from these trials have been complex and contrasting. The Fem-PrEP (pre-exposure prophylaxis) trial studying African women was discontinued early because of a lack of protection.\textsuperscript{44} Contrarily, the TDF2 study found an efficacy rate of about 62% for HIV prevention in both African men and women.\textsuperscript{45} The Partners PrEP study examined the use of daily oral tenofovir or tenofovir-emtricitabine in high-risk populations of sexually active women, men and HIV-discordant couples with an efficacy rate of approximately 75%.\textsuperscript{46}

A phase 1 clinical trial of 0.3% and 1% tenofovir vaginal gels in sexually active and sexually inactive HIV-negative and HIV-positive women found the gels to be safe, acceptable and well tolerated for a two-week twice daily course.\textsuperscript{47} A PK cross-over study comparing tenofovir vaginal gel and oral tablets found that gel dosing achieved lower serum concentrations but much higher vaginal tissue concentrations.\textsuperscript{48} The work suggested that topical gel should theoretically provide greater PrEP efficacy but noted that other factors had greater influence above the antiviral effect of tenofovir.

The Centre for the AIDS Program of Research in South Africa (CAPRISA) 004 trial assessed the effectiveness and safety of a 1% vaginal gel formulation of tenofovir for the prevention of HIV acquisition in women.\textsuperscript{33} A double-blind, randomized controlled trial was conducted comparing tenofovir gel (n = 445 women) with placebo gel (n = 444 women)
in sexually active, HIV-uninfected 18- to 40-year-old women in urban and rural KwaZulu-Natal, South Africa. The dosing strategy was based on the woman inserting a dose of gel within 12 hours before sex and a second gel dose as soon as possible and within 12 hours after sex, with a maximum of two doses within 24 hours. Overall tenofovir gel reduced HIV infection by approximately 39%, with the peak effectiveness observed after 12 months of the trial at 50% protection. Participants with high (>80%), intermediate (50–80%) and low (<50%) gel adherence showed varying degrees of protection of 54%, 38% and 28% respectively. Whilst the sample size and number of sites was relatively small in this study, it provided promising evidence that coital related dosing of tenofovir appears safe and effective in preventing HIV infection in women.

VOICE—Vaginal and Oral Interventions to Control the Epidemic was a major HIV prevention trial evaluating safety and efficacy of 3 ARV products: an oral tablet containing tenofovir, an oral tablet containing both tenofovir and emtricitabine and a tenofovir gel for vaginal administration. Despite promising results from the Partner PrEP trial, which examined both tenofovir only and tenofovir plus emtricitabine oral tablets taken once daily, the once-daily oral tenofovir only arm of VOICE was stopped early due to futility. The same occurred with the vaginal gel arm, which examined the daily administration of a 1% tenofovir gel, despite the CAPRISA-004 trial showing an efficacy of around 39%, where the gel was administered 12 hours before sex and a second dose as soon as possible (and within 12 hours) after sex. The result highlighted the importance of dosing regimens for the vaginal gel product.

Safety
Deeks assessed the short-term safety of tenofovir in 20 HIV-infected adults administered by intravenous infusion. In this phase 1/2 clinical study, tenofovir appeared to be safe and well tolerated, with the most frequently reported adverse events mild and transient (grade I) such as headache, dizziness, fatigue and nausea. Three moderate (grade II) adverse events were also reported of nausea, fatigue and abdominal pain, all of which resolved without discontinuation of the drug. Tenofovir formulated as a once-a-day 300 mg single tablet has been extensively studied for efficacy and safety for the treatment of HIV-1 infections. A 24-week investigation by Gilead into the safety of this tenofovir therapy showed a similar toxicity profile to that of placebo. A larger 600-patient Gilead Sciences Study GS-99-903 (Study 903) compared a combination treatment of tenofovir, lamivudine and efavirenz with a combination treatment of stavudine, lamivudine and efavirenz in antiretroviral-naive patients in a randomized, double-blind, parallel, placebo-controlled trial over 144 weeks. During Study 903, a decrease in bone mineral density at the spine and hip was seen in the first 48 weeks but was non-progressive over the remaining weeks. The A5224s trial has also recently reported that a tenofovir-emtricitabine therapy leads to a reduction in spine and hip bone mineral density within the first 48 weeks. Compared to other antiretrovirals the tenofovir-emtricitabine based therapy provided for a significant reduction in spine and hip bone mineral density. Study 903 found no significant nephrotoxicity or renal impairment, which had been reported previously among tenofovir-treated HIV patients. An additional 336-week open-label extension phase of Study 903 for 86 patients reported no renal impairment. A review by Cooper et al that assessed the findings of 17 clinical trials of tenofovir therapies, including Study 903, concluded that although the use of the drug was associated with a statistically significant loss of renal function, the clinical magnitude of this effect was modest. The authors did not feel that the use of tenofovir needed to be restricted provided there was regular monitoring of renal function.

During the HPTN 050 trial of a tenofovir gel, at least one adverse event was reported by 92% of participating women; 70% of the reports involved ‘reproductive system and breast disorders’ (according to MedDRA coding), predominantly involving the genital tract. Just under a third of the women (32%) using the gel experienced diarrhea and general gastrointestinal symptoms. There was no specific adverse event pattern in relation to gel concentration or frequency of use. One severe adverse event occurred, a case of pelvic inflammatory disease that was possibly product related and was successfully treated with antibiotics. One moderate adverse event, shallow vulvar ulcerations, resulted in the termination of further use of the gel for that participant. The most common adverse events were genital pruritus (23%), applicator site bruising (17%), applicator site erythema (17%) and vaginal discharge (15%). There was no difference in the levels of bone fracture among participants assigned to receive tenofovir gel and the placebo gel. In CAPRISA-004, use of 1% tenofovir vaginal gel was well-tolerated. While 94% of women reported at least one adverse event, there were no product-related increases in renal impairment or genital adverse events. Cases of diarrhea were reported by 17% of women, but these tended to be mild, rarely requiring medication. The vaginal gel arm of the MTN 001 trial had very limited adverse events, particularly in comparison to the oral and combination arms. Transient and mild symptoms were expressed as nausea (3%) and headache (2%).

Patient Preference and Place in Therapy
The efficacy of 1% tenofovir gel is fundamentally linked to adherence, and the statistics would suggest that women are unwilling or unable to consistently use the gel as an integral part of their sex life. During the CAPRISA 004 trial, consistent (≥80%) use of the gel both before and after intercourse provided a 54% decrease in the risk of HIV infection. The gel was half (28%) as effective against HIV infection if use of the gel was inconsistent (≤50%) with intercourse. Adherence promotion in the form of intensive monthly counselling and
motivational interviewing of participants only provided for overall adherence of 38% of women using the gel ≥80% before and after intercourse. The microbicidal community still need to address this problem of low adherence for vaginal gels. They must clearly understand what prevents gels from being an integral part of the sex life of at-risk women; otherwise such products will have only a limited place in prophylaxis.

Is a lack of acceptability for the gel, particularly among at-risk women, the root cause of this low adherence? Women have shown a clear preference for and have a high acceptance for vaginal gels. An early study among Brazilian women examined their preferences for vaginal antimicrobial contraceptives; there was clear preference for a gel (39.6%) compared to other dosage forms, such as creams and films.61 During the HPTN 050 trial,62 94% of participating women were fully adherent and said they definitely or probably would use the product if they were worried about being infected by or transmitting HIV, indicating that the gel was highly acceptable. Overall, the gel was liked by 79% of the women and 76% of male partners. However, a significant portion of these same women did report issues with the product that are already well-known disadvantages of vaginal gels. Leakage—before (41%), during (50%) and after (68%) sex—was the most common issue reported by the women. Non-intercourse-related leakage was also commonly reported. Several women found the gel messy to an unacceptable level. Some found the leakage significant, leaving them feeling moist and uncomfortable for considerable periods of time, compelling a more rigorous hygiene regime to compensate. Two thirds of women experienced leakage or messiness, while the remainder did not find the gel messy and did not experience significant leakage. Of sexually-active participants, 86% felt the gel provided for wetter sex, with a mixed reaction to whether or not this increased, decreased or made no difference to sexual pleasure. 90% of the women indicated either that the gel increased their sexual pleasure or that it made no difference.

The acceptability of the vaginal gel approach is clearly dependent on the effect the product has on the personal hygiene of the woman and on sexual intimacy with her partner. A recent review of vaginal HIV microbicides highlights clearly the importance and complexity the issue of wetness has in the acceptance of gel products in terms of personal hygiene, female preference, male preference and a women’s perception of her partner’s preference.63 This review highlights the sometimes contradictory findings into the preferences for gel attributes among women and men, as well as the type of sex (dry or wet) preferred and how this influences the choices women make in continuing to use certain vaginal products. Adherence is the single most important factor controlling the effectiveness of potent microbicide gels and adherence appears tied up in the complex issue of acceptability. The 1% tenofovir gel, and other microbical gels that may follow, will find a place in therapy not as a single therapy in the field of vaginal microbicides but one of a number of therapies, including rings,64,65 films,66,67 diaphragms,68,69 and tablets,70 which can offer women many different choices to meet their individual needs.

Conclusion

As no HIV vaccine will likely be available in the near future, there needs to be a push towards the development of HIV microbicide products that will reduce the rate of new HIV infections. The encouraging data from the CAPRISA 004 clinical trial may do just that. However, there is an overreliance on reverse transcriptase inhibitors (RTI), like tenofovir, for use as HIV microbicides and there needs to be a move towards developing and clinically testing other potential candidates, such as entry inhibitors, integrase inhibitors and protease inhibitors, as well as various peptide- and protein-based molecules. Furthermore, the microbicidal field needs to develop and clinically test a range of vaginal dosage forms, including gels, tablets, rings and films, because no one product is going to alleviate the adherence issues associated with the 1% tenofovir gel tested in the CAPRISA 004 study. A range of products needs to be made available to women, allowing them to choose the product(s) that best suits their (and their partners’) sexual needs. Therefore, the 1% tenofovir gel will not be the single HIV microbicide product available, but will be part of a much wider range of products, which consists of a number of different dosage forms containing a range of different active ingredients, allowing for a dosing regimen tailored towards the individual.

Author Contributions

Conceived the concept: CM, PB, IM. Analyzed the data: CM, PB, IM. Wrote the first draft of the manuscript: CM, PB, IM. Agree with manuscript results and conclusions: CM, PB, IM. Jointly developed the structure and arguments for the paper: CM, PB, IM. Made critical revisions: CM, PB, IM.

All authors reviewed and approved of the final manuscript.

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