

Identification of Personal Lubricants That Can Cause Rectal Epithelial Cell Damage and Enhance HIV Type 1 Replication *in Vitro*

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Abstract

Over-the-counter personal lubricants are used frequently during vaginal and anal intercourse, but they have not been extensively tested for biological effects that might influence HIV transmission. We evaluated the *in vitro* toxicity anti-HIV-1 activity and osmolality of popular lubricants. A total of 41 lubricants were examined and compared to Gynol II and Carraguard as positive and negative controls for toxicity, respectively. Cytotoxicity was assessed using the XTT assay. The MAGI assay with R5 and X4 HIV-1 laboratory strains was used to evaluate antiviral activity. The effect of the lubricants on differentiated Caco-2 cell monolayers (transepithelial electrical resistance, TEER) was also measured. None of the lubricants tested showed significant activity against HIV-1. Surprisingly, four of them, Astroglide Liquid, Astroglide Warming Liquid, Astroglide Glycerin & Paraben-Free Liquid, and Astroglide Silken Secret, significantly enhanced HIV-1 replication ($p < 0.0001$). A common ingredient in three of these preparations is polyquaternium-15. *In vitro* testing of a chemically related compound (MADQUAT) confirmed that this similarly augmented HIV-1 replication. Most of the lubricants were found to be hyperosmolar and the TEER value dropped approximately 60% 2 h after exposure to all lubricants tested. Cells treated with Carraguard, saline, and cell controls maintained about 100% initial TEER value after 2–6 h. We have identified four lubricants that significantly increase HIV-1 replication *in vitro*. In addition, the epithelial damage caused by these and many other lubricants may have implications for enhancing HIV transmission *in vivo*. These data emphasize the importance of performing more rigorous safety testing on these products.

Introduction

THE INCREASED INTEREST in the past few decades in an effective vaginal or rectal microbicide to reduce the transmission of HIV and other sexually transmitted infections (STIs) has resulted in several clinical trials. Unfortunately, a few trials have found an increase in the number of infections in the microbicide arm prompting a more rigorous approach to testing the safety of these products. At the same time, many over-the-counter (OTC) personal lubricants have been available for decades without testing the effect that repeated use of these products could have on HIV and STI transmission. There are hundreds of different sexual lubricants available on the market and over the Internet. Substances not specifically marketed as sexual lubricants are also commonly used,

especially in low-income households and developing parts of the world where people do not have access to and cannot afford to purchase sexual lubricants. But whether the use of lubricants poses a risk to sexual health is still unclear.

In addition to vaginal application, personal lubricants are commonly used during anal intercourse. HIV target cells such as lymphocytes, macrophages, and dendritic cells are found under the epithelium of the vagina/cervix and rectum.¹ Thus, a break in the integrity of the epithelium could provide a passageway for HIV to make contact with these cells. There is evidence that personal lubricants containing nonoxynol 9 (N-9) may disrupt the rectal epithelial lining and cause rectal sloughing leading to increased susceptibility to herpes simplex virus type 2 (HSV-2) infection in the mouse model.^{2–4} N-9 failed in Phase 3 clinical trials, presumably due to the

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drug-induced formation of localized genital lesions that may in fact promote virus transmission. There is also *in vitro* evidence that N-9 disrupts cervical epithelium.⁵ Consequently, the Food and Drug Administration (FDA) issued a final rule establishing new warning statements and other labeling information for all OTC vaginal contraceptive drug products containing N-9⁶ and many sexual lubricant manufacturers pulled products that contained N-9 off the market altogether.

However, extensive testing of OTC sexual lubricants has still not been performed. A few studies have addressed the role of osmolality in a small number of lubricants in preserving the integrity of the rectal epithelium. One such study concluded that hyperosmolar gels induce greater epithelial denudation and luminal secretion than isoosmolar gels.⁷ Some studies suggest that trauma or minor breaches may increase risk, whereas increasing evidence from circumcision trials and studies in sex workers suggest that proinflammatory conditions may be sufficient to increase risk.⁸ On the other hand, another recent report concluded that three OTC lubricants were active against HIV *in vitro* suggesting these formulations have the potential to prevent sexual transmission of HIV.⁹

We set out to further explore the latter claim by measuring the osmolality, *in vitro* toxicity, impact on epithelial cell integrity, and anti-HIV activity of a wide range of personal lubricants. We tested a majority of the lubricants identified in a recent online survey as personal lubricants that were likely to be used during protected and unprotected anal intercourse.¹⁰ Finally, our study reveals important information about four OTC lubricants that may facilitate the spread of HIV.

Materials and Methods

Products

We purchased 41 OTC water-based sexual lubricants as listed in Table 1. Additionally we used Carraguard (Population Council, New York, NY), D-PBS (Invitrogen, Grand Island, NY), and Gynol II Vaginal Contraceptive Jelly (Caldwell Consumer Health, LLC, Parsippany, NJ). Polybrene and poly[2-(dimethylamino)ethylmethacrylate] methyl chloride quarternary salt (MADQUAT) were purchased from SIGMA (St. Louis, MO).

Cell lines and viruses

TZM-bl cells, an engineered HeLa clone originally isolated from a human cervical adenocarcinoma, were obtained through the National Institute of Allergy and Infectious Diseases (NIAID) AIDS Research and Reference Reagent Program.¹¹ Caco-2 cells, derived from a colonic adenocarcinoma, were obtained through the American Type Culture Collection (ATCC; Rockville, MD). All the cell lines were cultured in D-MEM (Invitrogen) supplemented with 10% heat-inactivated fetal bovine serum (Invitrogen) and antibiotics at a final concentration of 50 units/ml of penicillin and 50 μ g/ml streptomycin (Invitrogen). For the seeding of Caco-2 cells, cells were grown and differentiated using the BD BioCoat HTS Caco-2 Assay System (BD Biosciences, Bedford, MA).

Two HIV-1 laboratory strains that use different HIV-1 coreceptors, CXCR4 or CCR5, were tested. The X4 HIV-1_{MN} (Lot #P3817 and P3950) and R5 HIV-1_{ADA-M} (Lot #P4186 and

P4193) laboratory strains were provided by Dr. J.D. Lifson at the AIDS and Cancer Virus Program, SAIC-Frederick, Inc., National Cancer Institute, Frederick, MD.

Toxicity and monolayer integrity testing

A colorimetric assay based on the reduction of a tetrazolium salt (2,3-bis[2-methoxy-4-nitro-5-sulphophenyl]-2H-tetrazolium-5-carboxanilide [XTT] from SIGMA was used to determine the cellular cytotoxicity in TZM-bl cells as described before.¹² Various serial dilutions of each lubricant were made in cell culture media and formulation or compound was added to the cells and incubated at 37°C, 5% CO₂ for 72 h. The assay was performed in TZM-bl cells in order to get a CC₅₀ value to use in the calculation of the therapeutic index before estimating the antiviral activity (IC₅₀) in the same cell line.

Changes in Caco-2 monolayer integrity were measured by transepithelial electrical resistance (TEER) using the 3-Day BD BioCoat HTS Caco-2 Assay System. Briefly, Caco-2 cells were grown on double chamber 24-well plates until differentiation was reached at a TEER value higher than 300 $\Omega \times \text{cm}^2$ as measured by an EVOM epithelial voltmmeter (World Precision Instruments, Sarasota, FL). Neat lubricants or formulations were added to the apical surface of the monolayer and resistance readings were measured at 0, 2, 4, and 6 h. Cells in growth media, Carraguard, D-PBS, or Gynol II versus media without cells (blank) were included as controls. To compare the loss of cell monolayer integrity, Gynol II with 2% N-9 was used as a positive control. Carraguard, cell culture media, and D-PBS were used as negative controls. The epithelial resistance was calculated by subtracting the ($\Omega \times \text{cm}^2$) of the blank from the ($\Omega \times \text{cm}^2$) of the treated wells.

Antiviral testing

Antiviral activity against HIV-1 was tested using the standardized TZM-bl-based multinuclear activated galactosidase indicator (MAGI) assay. Cells were seeded as described before¹³ and after 24 h incubation at 37°C, the culture supernatants were replaced with fresh culture media containing HIV-1 (approximately 100–200 focus forming units/well, which represents a multiplicity of infection of 0.001) and various serial dilutions of the test compounds in cell culture media added directly together. All the samples were diluted starting at the dilution that allowed cell viability greater than 80%. Carraguard served as a positive control for the antiviral experiments using HIV-1_{MN} since it has previously shown high selectivity against this strain *in vitro*.¹² After 72 h incubation, TZM-bl cells were fixed and stained with 5-bromo-4-chloro-3-indolyl-D-galactosidase (Invitrogen) as described previously.¹² The infected cells develop a blue color localized in the nuclei due to the cleavage by β -galactosidase (expressed in infected cells) of the 5-bromo-4-chloro-3-indolyl-D-galactosidase yielding an insoluble blue product. The positive cells are quantified on an AID ELISPOT plate reader (Cell Technology, Columbia, MD). The virus only controls reproducibly gave 100–200 positive (HIV-infected) cells.

Physicochemical testing

Measurements for osmolality and pH were performed for each lubricant or formulation. Two types of osmometry were

TABLE 1. MOST COMMERCIAL LUBRICANTS HAVE INSIGNIFICANT OR NO ANTIVIRAL ACTIVITY AGAINST HIV-1

Lubricant	Mean HIV-1 _{MN} TI (CC ₅₀ /IC ₅₀)	Mean HIV-1 _{ADA-M} TI (CC ₅₀ /IC ₅₀)	Osmolality (mOsm/kg)	pH
KY [®] Jelly ^a	2.8	2.3	2007	4.55
KY [®] Warming Jelly ^a	<3.8	<3.8	ND	4.50–6.50
KY [®] Tingling Jelly ^a	9.3	2.8	5047	3.61
KY [®] Sensual Silk ^{TM,a}	2.8	<1.6	5467	3.39
KY [®] Sensual Silk TM Warming ^a	<2.3	<2.3	ND	5.00–7.00
KY [®] Sensual Silk TM tingling Ultrage ^{®a}	<2.9	1.5	5381	3.36
KY [®] Natural Feeling Liquid ^a	8.5	<2.3	4523	3.86
Wet [®] Original Gel Lubricant ^b	1.7	4.2	3679	5.9
Wet [®] Light ^b	<1.8	2.2	3946	6.02
Wet [®] Warming ^b	<2.5	1.7	ND	6.0–7.5
Durex [®] Play Soothing ^c	4.8	4.9	1373	4.2
Durex [®] Play Warmer ^c	<5.4	<2.7	ND	4
Durex [®] Play Piña Colada ^c	<2.6	<2.6	ND	4.29
Durex [®] Play More ^c	>8.6	>2.3	1332	4.49
ID [®] Glide ^d	<0.7	<1.4	2901	5.2
ID [®] Juicy Lube Cherry ^d	2.3	<2.1	3030	5.35
ID [®] Pleasure ^d	2.7	<1.2	2898	5.26
ID [®] Sensation ^d	<2.2	<2.2	ND	5.95–6.5
Astroglide[®] Liquid^e	7.9	<3.2	8064	4.44
Astroglide [®] Gel ^e	3.3	1.7	2299	4.3
Astroglide[®] Warming Liquid^e	<1.9	<1.9	ND	6.45–6.73
Astroglide[®] Glycerin & Paraben-Free Liquid^e	11.2	<2.5	4806	4.54
Astroglide [®] Strawberry ^e	<4.8	2	ND	5.35
Astroglide[®] Silken Secret^{TM,e}	<2.5	<2.5	6121	4.73
Lifestyles [®] Liquid (with Aloe & Vit. E) ^f	39.3	<3.0	4229	6.3
Lifestyles [®] Excite Sensual Gel ^f	7.6	<5.0	3728	7.2
Lifestyles [®] Warm Lovin ^f	48.1	4.2	ND	5.24
Maximus ^g	9.4	1.8	6415	6.05
BabeLube ^h	7.2	13.3	19	6.78
Elbow Grease [®] Thin Gel ⁱ	<1.7	<1.7	2977	5.77
Slippery Stuff [®] Gel ^j	5.6	27.6	13	6.89
O'My [®] Natural Lubricant ^k	13	2.7	4348	5.46
Liquid Silk ^g	<2.0	<2.0	3167	5.26
Probe [®] Personal Lubricant ^l	<6.9	<6.9	341	7.67
Anal Lube TM Original Formula ^m	<2.5	2.5	3456	5.77
ForPlay [®] Gel-Plus ⁿ	<7.0	<7.0	9177	6.58
Gun Oil [®] H ₂ O ^o	<2.6	<2.6	3955	5.61
Duane Reade [®] Lubricating Jelly ^p	4.4	2.4	737	4.79
Moist Again TM Vaginal Moisturizing Gel ^q	0.7	0.7	187	5.68
Replens ^{®r}	>82.2	11.8	1491	2.98
FemGlide ^{TM,s}	20.6	12.4	15	6.13
Carraguard ^{TM,t}	>3587.0	>0.7	432	6.8

These results come from 2 or more independent experiments. Bold = enhancement in HIV-1 replication at high concentrations when compared to the virus control. ND = not determined.

^aJohnson & Johnson, Langhorne, PA.

^bTrigg Laboratories, Valencia, CA.

^cSSL International plc, London, UK.

^dWestridge Laboratories, Inc., Santa Ana, CA.

^eBioFilm, Inc., Vista, CA.

^fAnsell Limited, Richmond, Vic., Australia.

^gBodywise Limited, Isle of Wight, UK.

^hBabeland, Seattle, WA.

ⁱB. Cumming Company, Inc., Sun Valley, CA.

^jWallace O'Farrell, Inc., Puyallup, Wa.

^kO My Products, Inc., Vancouver, B.C., Canada.

^lDavryan Laboratories, Inc., Portland, OR.

^mCalifornia Exotic Novelties, Inc., Chino, CA.

ⁿTrimensa Pharmaceuticals, Newbury Park, CA.

^oEmpowered Products, Inc., Las Vegas, NV.

^pDuane Reade, Inc., New York, NY.

^qLake Consumer Products, Inc., Jackson, WI.

^rLil' Drug Store Products, Inc., Cedar Rapids, IA.

^sCooper Surgical, Inc., Puyallup, WA.

^tPopulaton Council, New York, NY.

performed. First, vapor pressure osmometry was performed (Vapro vapor pressure osmometer 5520 Wescor, Inc., Logan, UT). The device was calibrated with Opti-mole 100, 290, and 1000 mmol/kg osmolality standards. Measurements for a number of products were problematic, possibly due to volatile organics interfering with the thermocouple head preventing the reading. Follow-up measurements were then performed using freezing point depression osmometry (Advanced Instrumental Model 3250 freezing point osmometer, Norwood, MA). pH was determined using the Orion 4-Star Plus Benchtop pH/ISE Meter (Thermo Fisher Scientific) with an Orion 8235BN PerpHect Ross flat surface pH probe and calibrated using three points, pH 4.0, 7.0, and 10.0.

Statistical methods

In all experiments, each dilution of lubricant, formulation, or compound was tested in triplicate. The experiments were repeated at least twice. The CC_{50} (cytotoxicity from the XTT assay) and IC_{50} (virus inhibition from the MAGI assay) values were calculated using a dose-response-inhibition analysis on GraphPad Prism v5.0 software. The CC_{50}/IC_{50} ratio (therapeutic index, or TI) was calculated and those lubricants with TI values higher than 100 were considered to have significant antiviral activity. When an IC_{50} value was not reached due to lack of antiviral activity or enhancement of infection, the highest concentration of the lubricant tested was used as the IC_{50} value to determine the ratio and the TI was listed as less than the value obtained. If a CC_{50} value was not reached due to the lack of toxicity the TI was listed as higher than the value obtained. To examine viral replication enhancement we used linear regression to model the mean log concentration/dilution versus the mean percent of viral replication. The data were analyzed using SAS software.

Results

Based on the TI values against either R5 or X4 HIV-1 (Table 1), most lubricants were not significantly active ($TI < 100$) to conclude that they could be considered potential microbicides. Mild anti-HIV-1_{MN} activity was seen in Replens.

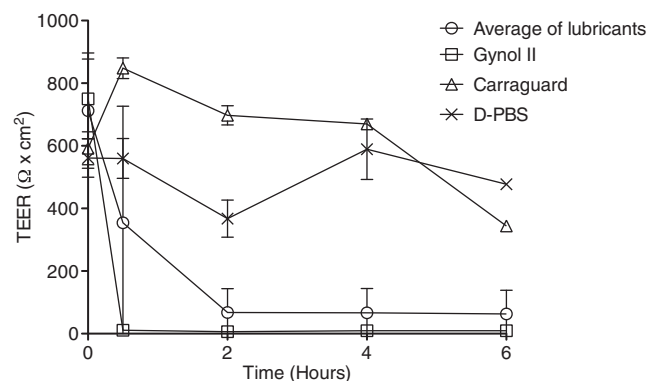


FIG. 1. Over-the-counter (OTC) lubricants reduce epithelial cell integrity. Caco-2 cell monolayers were incubated with each lubricant (triplicates of neat samples) and the TEER measured 2, 4, and 6 h later. Carraguard and Gynol II were included as controls. Data are shown as $\Omega \times \text{cm}^2$ (mean \pm SD of the triplicates) averaging the data for all of the lubricants versus the Gynol II, Carraguard, and D-PBS controls.

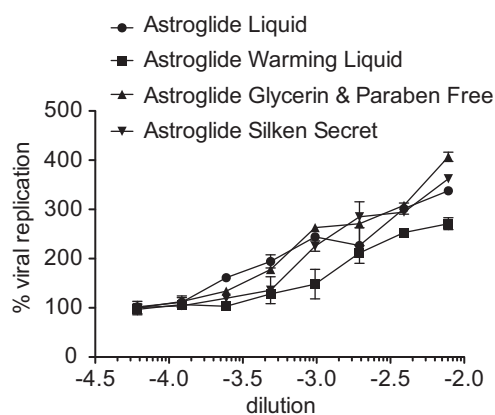


FIG. 2. Some lubricants enhance HIV-1 infection *in vitro*. HIV-1_{ADA-M} was added to TZM-bl cells in the presence of the various dilutions of the indicated Astroglide lubricants (triplicates per dilution). Infection was measured 72 h later and the data are presented as logarithm of the dilutions (mean \pm SD of the triplicates) versus percent viral replication, $p < 0.0001$.

None of these lubricants compared in activity to Carraguard, which has TI values > 3000 in this assay. Additionally, all the lubricants caused a drastic decrease in the TEER of Caco-2 monolayers (Fig. 1) after 2 h indicating the integrity of the monolayer was compromised.

Surprisingly, four Astroglide lubricants, Astroglide Liquid, Astroglide Warming Liquid, Astroglide Glycerin & Paraben-Free Liquid, and Astroglide Silken Secret, significantly enhanced both R5 (Fig. 2) and X4 (data not shown) HIV-1 replication. In each of the four instances, this enhancement was especially apparent at the higher end of the range of dilutions tested. Interestingly, these four Astroglide formulations shared a common ingredient that is not present in the other Astroglide formulations, polyquaternium (for three of them polyquaternium-15 is specified).

As a result, we wanted to test the antiviral activity of polyquaternium-15 on HIV replication; however, it was not commercially available. An alternative, related molecule that

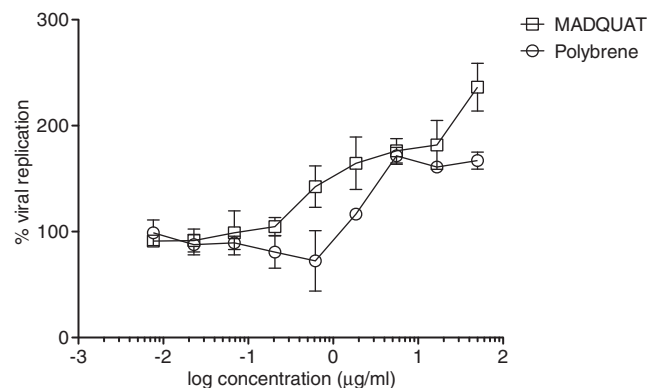


FIG. 3. The polyquaternium MADQUAT increases HIV-1 replication *in vitro*. TZM-bl cells were incubated with HIV-1_{ADA-M} in the presence or absence of the indicated concentrations of MADQUAT or polybrene; 72 h later, infection was measured. The data are displayed as logarithm of the compounds concentrations (mean $\mu\text{g}/\text{ml} \pm$ SD of the triplicates) versus percent viral replication, $p < 0.0001$.

also contains the poly[2-(dimethylamino)ethylmethacrylate] methyl chloride quarternary salt group (MADQUAT) was evaluated for its activity against HIV. This was compared to polybrene as a positive control since it is known to increase infection by improving retrovirus attachment to target cells.^{13–16} Figure 3 shows that MADQUAT enhanced HIV-1_{ADA-M} infection in a manner comparable to polybrene.

We were able to measure the osmolality of most of the products. One reason the vapor pressure osmometer could not read some of the samples may be due to volatile organics interfering with the thermocouple head preventing the reading. When using freezing point depression osmometry, many products did not freeze, presumably due to their high glycerol or propylene glycol contents. Consequently, those products underwent serial dilutions with water. The diluted, thoroughly mixed products were then measured. From the data we could gather, Slippery Stuff, FemGlide, BabeLube, and Moist Again Vaginal Moisturizing Lubricant were found to be hypoosmolar. Probe Personal, like the Carraguard control, was the only formulation found to be relatively isoosmolar. All remaining lubricants that were able to provide a reading were found to be hyperosmolar (Table 1).

Discussion

Despite the suggestions that some OTC lubricants have potential microbicidal activity, our evaluation of TI values for HIV-1 infection and more extensive toxicity testing of 41 lubricants—which is the majority of those identified as commonly-used in a survey of anal sex lubricant users—suggested otherwise.¹⁰ A few personal lubricants showed mild antiviral activity against HIV-1_{MN}, but none offered the level of protection afforded by the *in vitro* positive control Carraguard. Strikingly, not only did most not have antiviral activity, we identified four that dramatically amplified replication of both R5 and X4 HIV-1 strains. Previous studies documented anti-HIV-1 activity of Astroglide brand lubricants,¹⁰ but based on our findings, this appears to be due to the toxic effect of the product and not true antiviral effect. As seen in N-9 studies,^{5,6} although a compound has the potential to inactivate free HIV-1 particles and disrupt the cellular membrane of cells infected with HIV-1, the potential toxic effects outweigh the potential benefits. Herein we document that most of the 41 lubricants tested exhibited TI values that reflected the impact of cellular toxicity and not specific antiviral activity.

Recent studies have also shown a correlation between lubricant osmolality and rectal toxicity.⁶ Supporting this conclusion, our results show that a majority of the lubricants reduced the electrical resistance passing through the cellular monolayer indicating a loss of integrity, which may potentially increase the chances of HIV-1 transmission *in vivo*. Interestingly, a recent report showed that hyperosmolar formulations and surfactants such as GML (glycerol monolaurate) markedly increased the susceptibility of mice to HSV-2.¹⁷ Additionally, high levels of EDTA (a common ingredient in several lubricants) tended to increase the susceptibility of mice to HSV-2.¹⁷ Similarly, another group has reported that hyperosmolar lubricants are associated with cellular toxicity.¹⁸ A recent study also revealed that the use of some rectal lubricant products might increase susceptibility to rectal STIs. Specifically, 11.7% of subjects using lubricants tested positive for rectal STIs compared to only 4.5% of those who did not use

lubricants.¹⁹ Thus, certain lubricant formulations may increase the transmission of STIs that are known to enhance the spread of HIV.

An extraordinary observation herein was the significant enhancement of HIV-1 replication by low doses of 4 out of 41 lubricants. These include Astroglide lubricants, a very popular and commonly used brand. One common feature of three of these lubricants was the presence of a form of polyquaternium and we demonstrated that a related polyquaternium was able to enhance HIV replication *in vitro*. Polyquaternium is the International Nomenclature for Cosmetic Ingredients designation for several polycationic polymers that are used in the personal care industry. It has been recognized that polycationic reagents can aid viral infection processes *in vitro* by increasing viral attachment^{13–16} and reagents such as polybrene are widely utilized to increase the *in vitro* infectivity of several retroviruses including HIV-1.^{20,21}

None of the lubricants tested shows a potential for becoming a microbicide, thus we cannot advocate for any of these lubricants to be used as such based on our *in vitro* data. Additionally, many of the lubricants showed potential detrimental effects that might contribute to HIV transmission. This emphasizes the need for more rigorous testing of OTC personal lubricants as is typically applied to microbicides. It is also important to mention that our results are coming from *in vitro* studies and further studies looking at the effects of these lubricants *in vivo*, as well as more relevant studies correlating the use of these lubricants with the prevalence of STIs, are needed to clearly define the detrimental effects that lubricants may have on HIV and STI transmission.

Acknowledgments

We would like to thank Drs. J.W. Bess, Jr. and J.D. Lifson at the AIDS and Cancer Virus Program, SAIC-Frederick, Inc., National Cancer Institute, Frederick, MD for providing the HIV-1 laboratory strains used in our experiments. The following reagent was obtained through the NIH AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH: TZM-bl from Dr. John C. Kappes, Dr. Xiaoyun Wu, and Tranzyme, Inc. This work was supported by the Swedish Ministry of Foreign Affairs and the Swedish International Development Cooperation Agency.

Author Disclosure Statement

No competing financial interests exist.

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