2-2022

HIV-1 RNA genital tract shedding after cryotherapy for visual inspection with acetic acid-positive cervical lesions in western Kenya

Anne Bocage
Warren Alpert Medical School, USA

Elkanah Omenge
Aga Khan University, elkanah.omenge@aku.edu

Tao Liu
Brown University, USA

Peter Itsura
Moi University, Kenya

Philip Tonui
Moi University, Kenya.

See next page for additional authors

Authors

Anne Bocage, Elkanah Omenge, Tao Liu, Peter Itsura, Philip Tonui, Kapten Muthoka, Stephen Kiptoo, Soya S. Sam, Angela Caliendo, and Susan Cu-Uvin

3 Systemic and Local Pharmacokinetics of DARE-BV1, a Novel Single Dose 2% Clindamycin Phosphate Vaginal Gel for the Treatment of Bacterial Vaginosis

MS[1], David Friend[2]
[1]Daré Bioscience, Inc, [2]Dare Bioscience

OBJECTIVES: DARE-BV1 is a novel, highly viscous single dose 2% clindamycin phosphate vaginal gel being investigated as a new treatment for bacterial vaginosis. In a recently completed large, randomized multi-center, placebo-controlled study, DARE-BV1 demonstrated a clinical cure of 70.5% vs. 35.6% in the placebo group ($p < 0.001$) at Days 21-30. The objective of this study was to determine the systemic and vaginal pharmacokinetics (PK) of DARE-BV1.

METHODS: Twenty-one (21) healthy adult women volunteers were recruited at a single site (ICON Early Phase Services, San Antonio, TX, USA). One subject terminated early due to potential COVID-19 exposure. At the Screening Visit, past medical and gynecological histories were collected/evaluated. Additionally, the following samples/tests were performed and collected: Affirm Vaginal Pathogens DNA Direct Probe test (VAGDNA) for *Candida* species, *Gardnerella vaginalis*, and *Trichomonas vaginalis*, tests for gonorrhea and chlamydia, human papillomavirus (HPV) test. Study drug (5 g of 2% clindamycin phosphate vaginal gel, 100 mg clindamycin) was applied intravaginally on Day 1 at the study clinic. Subjects had blood draws for plasma clindamycin concentrations taken at 0 hours (pre-dose) and then at 2, 4, 6, and 8 hours (±15 minutes) post-dose on Day 1 and at 24, 48, 72, 96, 120, and 144 hours (±2 hours) post-dose (Days 2 through 7). In addition, samples for vaginal clindamycin phosphate concentrations were collected once daily on Days 1 through 7 (with the Day 1 sampling done pre-dose). Plasma concentrations of clindamycin were assessed using a validated LC-MS/MS method with a lower limit of quantitation (LOQ) of 0.5 ng/mL. The concentration of clindamycin phosphate from vaginal swabs was measured by extracting the swabs followed by HPLC analysis. The LOQ for this method was 2.8 μg/g.

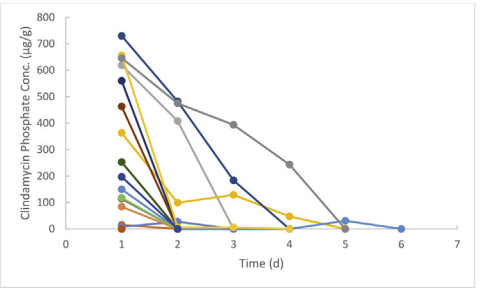
RESULTS: The plasma PK parameters collected are shown in Table 1. The C_{max} and AUC_{last} values are somewhat higher than those observed following a single or multiple doses of vaginal Cleocin, a currently approved clindamycin-based product for the treatment of bacterial vaginosis. They are also higher than those observed following vaginal administration of Clindesse, another clindamycin-based product approved for the treatment of bacterial vaginosis. T_{last} measured is consistent with a prolonged release of clindamycin phosphate from the gel. Vaginal concentrations of clindamycin phosphate are shown for all 21 subjects in Figure 1.

CONCLUSIONS: The plasma PK data as well as the vaginal clindamycin phosphate concentrations over time suggest that properties of DARE-BV1 maintain the drug at the site of action as compared to the other clindamycin-based products, maximizing the overall efficacy of the product for the treatment of BV. These findings may account for the relatively high efficacy of DARE-BV1 compared with other vaginal products used to treat BV.

Table 1 Plasma PK parameters following a single dose of DARE-BV1

Parameter	T_{max} (h)	C_{max} (ng/mL)	T_{last} (h)	C_{last} (ng/mL)	AUC_{last} h ng/mL)
Mean (± SD)	16.8 (22.4)	69.2 (76.4)	66.3 (35.3)	3.5 (3.6)	1,179 (980)

Figure 1.



4 HIV-1 RNA Genital Tract Shedding After Cryotherapy for Visual Inspection with Acetic Acid-Positive Cervical Lesions in Western Kenya

Anne Bocage[1], Omenge Orang'o[2], Tao Liu[3], Peter Itsura[2], Philip Tonui[2], Kapten Muthoka[2], Kiptoo Stephen[4], Soya S. Sam[5], Angela Caliendo[3], Susan Cu-Uvin[3]
[1]Warren Alpert Medical School, [2]Moi University, [3]Brown University, [4]Ampath Oncology Institute, [5]The Miriam Hospital

OBJECTIVES: To quantify genital tract HIV-1 RNA (GT-HIV RNA) shedding among women living with HIV (WLHIV) before and after cryotherapy treatment for visual inspection with acetic acid (VIA) positive cervical lesions.

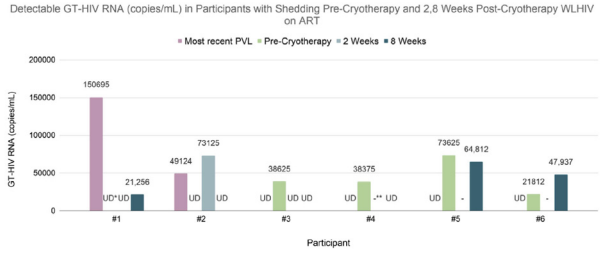
METHODS: We conducted a prospective, longitudinal study of 39 WLHIV on antiretroviral treatment (ART) undergoing cryotherapy for VIA positive lesions in Kenya from 2015-2017. Eligibility for cryotherapy were lesions that covered <75% of the cervix, with clear margins, no extension into the endocervix and no satellite lesions. Most recent plasma viral load (PVL) was collected from medical records. Endocervical secretions (TearFlo strips) were collected before cryotherapy and at two-weeks and eight-weeks follow-up visits. Abbott Realtime HIV-1 assay quantified GT-HIV RNA in participants before and after cryotherapy.

RESULTS: Detectable GT-HIV RNA was found in 4/39 (10%) participants pre-cryotherapy, 1/30 (3.3%) and 3/26 (11.5%) participants at the 2- and 8-weeks post-cryotherapy, respectively. Only 6/39 (13%) participants had detectable GT-HIV RNA at any point during the study. 2/6 had recent high PVL (range: 49,124-150,695 copies/mL) within 3 months of starting the study and detectable GT-HIV RNA at follow-up visits. 4/6 had undetectable recent PVL within 3-11 months of the study but each had detectable GT-HIV RNA pre-cryotherapy. The mean GT-HIV RNA among 4/39 WLHIV with shedding at pre-cryotherapy was 43,109 (range: 21,812-73,625) copies/mL. Only one participant had GT-HIV RNA (73,125 copies/mL) at 2-weeks post-cryotherapy (N=30); she had no shedding pre-cryotherapy but had a PVL of 49,124 copies/mL 3 months before the study. The mean GT-HIV RNA at 8-weeks post-cryotherapy (N=26)

was 44,668 (range: 21,256-64,812) copies/mL among three participants. One of the 3 had high PVL of 150,695 copies/mL 3 months prior to cryotherapy while 2/3 had GT-HIV RNA shedding at baseline despite undetectable most recent PVL. However, their undetectable PVL was 8-11 months prior to cryotherapy which may not accurately reflect PVL at baseline.

CONCLUSIONS: The majority of GT-HIV RNA shedding was detected before cryotherapy. This finding suggests that cryotherapy was not the primary cause of GT-HIV RNA shedding. Non-adherence to ART might have played a major role. The small sample size and failure to perform paired GT-HIV RNA and PVL tests at each visit are limitations of the study. Further research on the effect of cryotherapy on GT-HIV RNA shedding in ART non-adherent compared to ART-adherent WLHIV is needed.

Figure 1 – Cervical HIV-RNA Shedding During Any Visit Pre- and Post-Cryotherapy Treatment



*UD = Undetectable. Abbott Realtime HIV-1 assay quantified GT-HIV RNA with a detection range of 40 copies/mL to 10 million copies/mL.
**- = Participant did not attend the visit.

5 A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oteseconazole (VT-1161) Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis (VIOLET)

Karen Person[1], Stephen Brand[2], Thorsten Degenhardt[2], Stacey Curelop[3], Jack Sobel[4], Gilbert Donders[5]
[1]Selenity Therapeutics, [2]Mycovia Pharmaceuticals, [3]Mycovia Pharmaceuticals, Inc, [4]Wayne State University, [5]Femicare

OBJECTIVES: RVVC affects nearly 138 million women globally each year. Currently there are no FDA approved treatment options. Two Phase 3 studies evaluated the efficacy and safety of Oteseconazole (VT-1161) in the treatment of women with recurrent vulvovaginal candidiasis (RVVC).

METHODS: 656 patients with a history of RVVC (3 or more acute episodes within the previous 12 months) were enrolled at 181 centers in 11 countries. Patients were required to present with a vulvovaginal signs and symptoms score of ≥3 and a positive KOH. Following treatment of the presenting acute infection with fluconazole, patients were randomized to 1) 150 mg VT-1161 once-daily for 7 days, then 150 mg once-weekly for 11 weeks or 2) matching placebo regimen for 12 weeks. Patients were followed for 48 weeks.

RESULTS: Both studies achieved the primary efficacy endpoint by demonstrating significant differences between oteseconazole and placebo for the proportion of subjects with ≥1 culture-verified acute VVC episode through the 48-week Maintenance Phase in the ITT Population. Specifically, over 90% of women randomized to receive oteseconazole did not experience a recurrence during the 48-week maintenance phase compared to approximately 40% in the control group ($p < 0.001$).

Study completion was high and similar in both oteseconazole and placebo groups. Premature study discontinuations were similar between groups and there were no notable differences in demographics and baseline characteristics.

Subject compliance was high with no notable differences between treatment groups. The percentage of subjects who had ≥1 treatment-emergent adverse event (TEAE) was similar in the oteseconazole and placebo groups. The most frequently reported individual TEAEs were nasopharyngitis, bacterial vaginosis, urinary tract infection, upper respiratory tract infection, sinusitis, headache, cystitis, and back pain. The majority of subjects experienced either mild or moderately severe TEAEs. There were no drug-related SAEs and no evidence of adverse effects on pregnancy outcomes, liver function or QT intervals.

CONCLUSION: Oteseconazole oral dosing was shown to be effective in the treatment of RVVC and prevention of recurrence of acute VVC episodes during the Maintenance Phase through Week 48. Oteseconazole was safe and well-tolerated.

6 Sexually Transmitted Infections in Pregnant People living with Human Immunodeficiency Virus: Temporal Trends, Demographic Correlates and Association with Preterm Birth

Marisa Young[1], Carly Broadwell[2], Deborah Kacanek[3], Ellen Chadwick[4], Jennifer Jao[5], Anna-Barbara Moscicki[6], Kathleen Powis[7], Katherine Tassiopoulos[8], Lynn Yee[9], Lisa Haddad[10]
[1]Emory University, [2]Center for Biostatistics in AIDS, [3]Research Harvard TH Chan School of Public Health, [4]Ann & Robert H. Lurie Children's Hospital of Chicago, [5]Northwestern Feinberg School of Medicine, [6]UCLA, [7]Massachusetts General Hospital, [8]Harvard T. H. Chan School of Public Health, [9]Northwestern University Feinberg School of Medicine, [10]The Population Council

OBJECTIVES: Little is known about the trends and determinants of sexually transmitted infections (STIs) among pregnant people living with HIV (PLHIV). We describe temporal trends and to identify factors associated with *Chlamydia trachomatis* (CT), *Neisseria gonorrhea* (NG), syphilis and *Trichomonas vaginalis* (TV) diagnosed in pregnancy and evaluate associations of STIs with preterm birth (PTB; defined as delivery <37 weeks' gestation) among US PLHIV.

METHODS: The Surveillance Monitoring for ART Toxicities (SMARTT) dynamic cohort of the Pediatric HIV/AIDS Cohort Study (PHACS) network enrolls pregnant PLHIV at 21 clinical sites in the US. PLHIV delivering from 2010-2019 were included. Multifetal gestations were excluded from PTB analyses. Method of STI diagnosis was not abstracted. Multivariable log-binomial GEE models were used to estimate the association of calendar year with each STI, controlling for confounders. Multivariable Poisson GEE models were used to estimate the association of demographic and clinical factors with each STI. Stepwise regression with backwards elimination was used for model selection, beginning with factors with $p<0.2$ in univariable models. Multiple imputation was used as a sensitivity analysis for the TV model. Log-binomial GEE models were fit to estimate the association of each STI with PTB.

RESULTS: There were 2,240 pregnancies among 1,821 PLHIV evaluated in the analyses of STI trends and correlates and 2,146 pregnancies among 1,785 PLHIV included in the PTB analyses. Median age at delivery was 29.2 years, 67% of participants were Black or African American and median gestational age at entry into prenatal care was 10.7 weeks. Among the 2,240 pregnancies, STI prevalence