ClinicalTrials.gov

Topical Metronidazole and Miconazole Co-formulated Vaginal Suppositories for Preventing Vaginal Infections in HIV-seronegative Women

Sponsor:
National Institute of Allergy and Infectious Diseases (NIAID)

Information provided by (Responsible Party):
National Institute of Allergy and Infectious Diseases (NIAID)

Purpose

This research study is about vaginal infections such as bacterial vaginosis, yeast infections, and trichomoniasis. Usually, these infections can be treated with medication, but sometimes they come back after treatment. Researchers want to know if using vaginal suppositories can decrease the risk of vaginal infections. Participants will include 234 women who are sexually active (greater than or equal to 4 episodes of sex with men during the past month), HIV-negative, 18 to 45 years old, with bacterial infection [vaginosis and/or vulvovaginal candidiasis (VVC) and/or Trichomonas vaginalis] detected by laboratory testing at a screening visit. Women will receive vaginal suppositories containing drug or inactive ingredients (placebo). Participation in the study will be about 12 months. Study procedures include: urine and blood tests, physical exams, and questionnaires.

<table>
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<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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</thead>
<tbody>
<tr>
<td>Bacterial Vaginosis</td>
<td>Drug: Neo-Penotran® Forte (active ingredient Metronidazole &amp; Miconazole Nitrate)</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>Drug: Placebo</td>
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<tr>
<td>Trichomoniasis</td>
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</table>

Study Type: Interventional

Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator)
Primary Purpose: Prevention
Official Title: A Double-Blind, Randomized Trial of Monthly Treatment With Topical Metronidazole and Miconazole Co-formulated Vaginal Suppositories Versus Placebo for Preventing Vaginal Infections in HIV-seronegative Women

Further study details as provided by National Institute of Allergy and Infectious Diseases (NIAID):

Primary Outcome Measures:

- Efficacy of Monthly Periodic Presumptive Treatment (PPT) Using Metronidazole With Miconazole Intravaginal Suppositories Versus Matching Placebo Nightly for Five Nights Each Month for Preventing Vulvovaginal Candidiasis (VVC). [ Time Frame: Months 2, 4, 6, 8, 10, and 12. ] [ Designated as safety issue: No ]
  
  Percentage of follow-up visits (Months 2, 4, 6, 8, 10, 12) positive for VVC based on the presence of fungal elements (pseudohyphae, blastoconidia, or both) on vaginal saline wet mount plus a positive culture showing yeast on Sabouraud's agar.

- Efficacy of Monthly Periodic Presumptive Treatment (PPT) Using Metronidazole With Miconazole Intravaginal Suppositories Versus Matching Placebo Nightly for Five Nights Each Month for Preventing Bacterial Vaginosis (BV). [ Time Frame: Months 2, 4, 6, 8, 10, and 12. ] [ Designated as safety issue: No ]
  
  Percentage of follow-up visits (Months 2, 4, 6, 8, 10, 12) positive for BV as determined by applying standard microscopic scoring criteria (Nugent's criteria) to vaginal Gram stained slides. BV is diagnosed when the score is greater than or equal to 7.

Secondary Outcome Measures:

- Efficacy of Monthly Periodic Presumptive Treatment (PPT) Using Metronidazole With Miconazole Intravaginal Suppositories Versus Placebo for Preventing Any Vaginal Infection (a Combined Endpoint Including BV, VVC, and Trichomonas Vaginalis Infection). [ Time Frame: Months 2, 4, 6, 8, 10, and 12. ] [ Designated as safety issue: No ]
Percentage of follow-up visits (Months 2, 4, 6, 8, 10, 12) positive for any of three vaginal infections (BV, VVC, Trichomonas vaginalis infection).

- Efficacy of Monthly Periodic Presumptive Treatment (PPT) Using Metronidazole With Miconazole Intravaginal Suppositories Versus Matching Placebo Nightly for Five Nights Each Month for Preventing BV by Clinical Criteria (Amsel's Criteria). [Time Frame: Months 2, 4, 6, 8, 10, and 12.] [Designated as safety issue: No]

Percentage of follow-up visits (Months 2, 4, 6, 8, 10, 12) positive for BV by clinical criteria (Amsel's criteria).

Enrollment: 234

Study Start Date: April 2011

Study Completion Date: August 2013

Primary Completion Date: August 2013 (Final data collection date for primary outcome measure)

<table>
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<th>Arms</th>
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<tr>
<td>Experimental: Arm 1</td>
<td>Drug: Neo-Penotran® Forte (active ingredient Metronidazole &amp; Miconazole Nitrate) Neo-Penotran® Forte (active ingredient Metronidazole &amp; Miconazole Nitrate), co-formulated vaginal suppositories containing metronidazole 750 mg with miconazole 200 mg and excipients (Witepsol S 55). Witepsol S 55 is a hard fat suppository base. Such bases consist mainly of triglyceride esters of the higher saturated fatty acids along with varying proportions of mono- and diglycerides. 117 subjects receive nightly for 5 consecutive nights each month.</td>
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<tr>
<td>Placebo Comparator: Arm 2</td>
<td>Drug: Placebo Placebo vaginal suppositories, identical in appearance to the active product; contains Witepsol S 55, Titanium Dioxide and</td>
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</table>
Placebo suppositories nightly for five consecutive nights each month; 117 Subjects.

D+C yellow #10 with no metronidazole or miconazole. 117 subjects receive nightly for 5 consecutive nights each month.

**Detailed Description:**

Vaginal infections including bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and Trichomonas (T.) vaginalis are common and have been associated with increased risk of HIV and other sexually transmitted infections (STIs) in multiple prospective studies. Effective interventions for prevention of vaginal infections could substantially reduce the risk of HIV and other STIs in women. A recently completed trial has demonstrated that monthly periodic presumptive treatment (PPT) can reduce vaginal infections and promote Lactobacillus colonization. However, the oral regimen of metronidazole 2 grams plus fluconazole 150 mg was not sufficiently effective to warrant moving to Phase III HIV/STI prevention trials using this intervention. The identification of more efficacious regimens for reducing vaginal infections is a crucial step towards the development of inexpensive, female-controlled, non-coitally dependent HIV/STI risk reduction interventions for women. There is growing evidence that higher doses and longer courses may be more effective for treatment of vaginal infections than single-dose therapy. The overall goal of this protocol is to conduct a randomized, double-blind, placebo-controlled trial to test the efficacy of monthly PPT with topical metronidazole 750 mg plus miconazole 200 mg (co-formulated suppositories) versus matching placebo suppositories nightly for five nights each month for reducing the rates of BV and VVC among HIV-seronegative women. This regimen could produce sufficient reductions in vaginal infections to support its use in Phase III HIV and STI prevention trials. The study participants will include 234 women who are sexually active (greater than or equal to 4 episodes of heterosexual intercourse during the past month), HIV-seronegative, 18 to 45 years old, with BV and/or VVC and/or T. vaginalis detected by laboratory testing at a screening visit. There will be two study arms. The treatment arm (117 subjects) will receive PPT with intravaginal metronidazole 750 mg plus miconazole 200 mg (co-formulated suppositories) for five consecutive nights each month. The placebo arm (117 subjects) will receive PPT with identical placebo intravaginal suppositories for five consecutive nights each month. Individual participants will be in the study for one year.

**Eligibility**

Ages Eligible for Study: 18 Years to 45 Years
Genders Eligible for Study: Female
Accepts Healthy Volunteers: No

**Criteria**

Inclusion Criteria:
Informed consent obtained and informed consent form (ICF) signed.

Female, aged 18-45 years.

Sexually active with greater than or equal to 4 episodes of sex with a male partner during the past month.

Human immunodeficiency virus (HIV)-seronegative on both HIV tests in parallel screening.

Presence of bacterial vaginosis (BV) and/or vulvovaginal candidiasis (VVC) and/or T. vaginalis infection at screening:
   a. BV: Microscopic criteria (Nugent's score greater than or equal to 7)
   b. VVC: Fungal elements (pseudohyphae, blastoconidia, or both) on vaginal saline wet mount plus a positive culture showing yeast on Sabouraud's agar.

Able and willing to comply with study visit schedule and procedures during the 12-month period of follow-up.

Able and willing to abstain from sex or to use non-latex condoms (provided) for 24 hours following insertion of each vaginal suppository.

Willing to abstain from alcohol during, and for 48 hours after, treatment.

Plan to remain in study area for the next year.

Agree to not participate in other research studies involving drugs, medical devices, or vaginal products for the duration of study.

Exclusion Criteria:

Currently pregnant (positive urine Beta-Human Chorionic Gonadotropin (hCG) or planning to conceive during the next 12 months (by self-report).

Currently breastfeeding.

Within first 3 months post-partum.

Current menstruation - women who are currently menstruating may be enrolled following the completion of menses.

History of 4 or more episodes of treatment for any vaginal infection in the past 12 months. This would be a cumulative total, including any treatment for bacterial vaginosis (BV) and/or vulvovaginal candidiasis (VVC) and/or Trichomonas vaginalis (TV) and/or syndromic.

History of medical condition that would contraindicate use of the study product
   a. Porphyria
   b. Epilepsy
c. Serious liver disease or signs and symptoms consistent with serious liver disease including jaundice, ascites, esophageal varices, encephalopathy, and bleeding disorders.

d. Renal failure

- History of adverse reaction to the study medications (intravaginal metronidazole or miconazole).
- Current use of medication that may interact with the study drug (due to vaginal absorption of study drug)
  a. Warfarin
  b. Phenytoin
  c. Phenobarbital
  d. Disulfiram
  e. Cimetidine
  f. Lithium
  g. Astemizole
  h. Terfenadine

- Current use of oral or intravaginal antifungal medication.
- Current use of oral or intravaginal metronidazole, tinidazole, or clindamycin.
- Current use of latex diaphragm.
- As determined by the investigator, a medical condition or situation exists such that study participation would not be advisable.

Locations

United States, Alabama

University of Alabama at Birmingham Medical Center
Birmingham, Alabama, United States, 35294-0007

Kenya

Women’s Health Project - Ganjoni Municipal Clinic
Mombasa, Coast, Kenya

University of Nairobi - Center for STD/HIV Research & Training
Nairobi, **Kenya**

University of Nairobi - **Kenya** AIDS Vaccine Initiative

Nairobi, **Kenya**

**Sponsors and Collaborators**

National Institute of Allergy and Infectious Diseases (NIAID)

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**Responsible Party:** National Institute of Allergy and Infectious Diseases (NIAID)

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[History of Changes](https://clinicaltrials.gov/ct2/show/NCT01230814/history)

**Other Study ID Numbers:** 09-0070 DMID STI CTG 09-0070 PVI

**Study First Received:** October 28, 2010

**Results First Received:** August 14, 2014

**Last Updated:** September 26, 2014

**Health Authority:**

Kenya: Ministry of Health  
United States: Federal Government  
United States: Food and Drug Administration  
United States: Institutional Review Board

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**Keywords provided by National Institute of Allergy and Infectious Diseases (NIAID):**

Bacterial vaginosis, metronidazole, miconazole, vulvovaginal candidiasis, trichomonas vaginalis, women, **Kenya**

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**Additional relevant MeSH terms:**

- **Candidiasis**  
- **Miconazole**  
- **Trichomonas Infections**  
- **14-alpha Demethylase Inhibitors**  
- **Vaginosis, Bacterial**  
- **Anti-Infective Agents**  
- **Bacterial Infections**  
- **Antifungal Agents**  
- **Genital Diseases, Female**  
- **Antiparasitic Agents**  
- **Mycoses**  
- **Antiprotozoal Agents**
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