

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Incidence and Factors Associated with Asymptomatic Gonococcal and Chlamydial Infection among US Navy and Marine Corps Men Infected With the Human Immunodeficiency Virus
<b>AUTHORS</b>	Carpenter, Robert; Refugio, Oliver; Adams, Nehkonti; O'Brien, Kevin; Johnson, Mark; Groff, Harold; Maves, Ryan; Bavaro, Mary; Crum-Cianflone, Nancy

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Alicen Burns Spaulding, PhD, MPH University of Minnesota School of Public Health Division of Epidemiology and Community Health
<b>REVIEW RETURNED</b>	13-Mar-2013

<b>THE STUDY</b>	My primary concern with this article is its unique contribution. The authors do not sufficiently document the extensive amount of work that has been conducted and published on STI infection among HIV-positive military members from the United States Military's Tri-Service AIDS Clinical Consortium Natural History Study and in particular the article by Spaulding, et al. (reference #20 in this manuscript) which directly answers the same research question the authors appear to have for this manuscript. They need to clarify how this manuscript contributes unique information to this research question.
<b>RESULTS &amp; CONCLUSIONS</b>	I do not feel that the authors sufficiently discussed previously findings from this literature.

<b>REVIEWER</b>	Anne Rompalo, M.D., Sc.M. Professor of Medicine Johns Hopkins School of Medicine Baltimore, MD USA  No competing interests
<b>REVIEW RETURNED</b>	15-Mar-2013

<b>GENERAL COMMENTS</b>	Very nicely written manuscript with a frank, honest discussion and conclusion. Only concern is the small sample size. Nonetheless, the data are convincing and support screening for STIs among HIV infected individuals based on risk not symptoms.
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<b>REVIEWER</b>	LTC Wade Aldous, PhD, D(ABMM) Chief, Microbiology Dept of Health Support Services U.S. Army Medical Department Center and School
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	I have no competing interests.
<b>REVIEW RETURNED</b>	18-Mar-2013

<b>THE STUDY</b>	<p>Is the overall study design appropriate and adequate to answer the research question?</p> <p>Would suggest changing the title and focus towards identification of asymptomatic extra-genital infections. As noted by the single positive urethral GC isolate, most cases would have been symptomatic in the first place.</p> <p>This study provides a snapshot in time, which may not fully represent the continuum of infections. Dr Rieg's article in AIDS PATIENT CARE and STDs performs a similar study with patient follow-up at 6 and 12 months. This is important because it provides stronger evidence for the identification of factors associated with infection.</p> <p>Many recent articles note the increased amount of risk taking in the younger population. It would be useful to stratify the incidence by age and other survey factors. Additionally, the surveys might have helped answer more questions by indicating the total number of partners and regularity of sexual activities, the total number of partners that may already be HIV positive, the number of partners with another known STI, etc. 60% of the respondents mentioned more than 1 partner and 62% identify with at least weekly sexual activity. These are probably the individuals with the higher incidence of infection.</p> <p>The study design indicates HIV patients that are asymptomatic and the results show the incidence rate or a percentage of those patients that are actually harboring an infection. This is a bias against any patients that were symptomatic in one or more locations but still asymptomatic in at least one location. Adding these individuals to the population would give true prevalence at each tested anatomic location. This study group is essentially too narrow.</p> <p>Are the patients representative of actual patients the evidence might affect? The title of the manuscript states "US military men", which would lead the reader to believe that all services are represented, but the Materials and methods section only identifies US Navy and Marine Corps personnel.</p> <p>Are the methods adequately described? Based upon the methods, all patients that decided to participate in the program would have had urine, rectal, and pharyngeal specimens submitted when meeting with their provider, but the results section notes difficulties in getting some specimens. There is no information as to how many specimens were collected initially vs having to return to the clinic to provide a specimen, nor is there any information on the timing of specimen collection compared to when the questionnaires were completed. This could have some bearing on the positivity rate.</p> <p>Although not possible at this junction, future studies may want to utilized self collected specimens, which of late are showing great promise in efficiency of testing.</p>
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	<p>Are the abstract/summary/key messages/limitations accurate? The abstract objective states that data regarding GC and Ct in military populations are lacking, which is true, but a pubmed search using chlamydia gonorrhea military culled out 26 articles. Only the most recent one is listed in the references.</p> <p>The conclusions section of the abstract describes a high prevalence of extragenital infection among HIV positive men. This research only describes testing asymptomatic patients, whereas a true prevalence would identify ALL extragenital infections in HIV positive men, both symptomatic and asymptomatic. The usage of the term prevalence in this manuscript should really be changed to incidence instead.</p> <p>Are the statistical methods described? Are they appropriate? Recommend changing prevalence to incidence as noted above.</p> <p>Are the references up to date and relevant? (If not, please provide details of significant omissions below.)</p> <p>Recommend including the following references as they relate to the research question.</p> <p>AIDS Patient Care STDS. 2008 Dec;22(12):947-54. Asymptomatic sexually transmitted infections in HIV-infected men who have sex with men: prevalence, incidence, predictors, and screening strategies. Rieg et al</p> <p>Clin Infect Dis. 2009 Nov 15;49(10):1532-5. High prevalence of anorectal chlamydial infection in HIV-infected men who have sex with men in Switzerland. Dang et al</p> <p>Sex Transm Dis. 2010 Dec;37(12):771-6. STD screening of HIV-infected MSM in HIV clinics. Hoover et al</p> <p>MMWR Morb Mortal Wkly Rep. 2009 Jul 10;58(26):716-9. Clinic-based testing for rectal and pharyngeal Neisseria gonorrhoeae and Chlamydia trachomatis infections by community-based organizations--five cities, United States, 2007. Centers for Disease Control and Prevention (CDC).</p> <p>Sex Transm Dis. 2012 Jun;39(6):482-4. Sentinel surveillance for pharyngeal chlamydia and gonorrhea among men who have sex with men--San Francisco, 2010. Park et al.</p> <p>Sex Transm Dis. 2011 Dec;38(12):1107-9. Self-screening for Neisseria gonorrhoeae and Chlamydia trachomatis in the human immunodeficiency virus clinic--high yields and high acceptability. Soni S, White JA.</p>
<b>RESULTS &amp; CONCLUSIONS</b>	<p>Do the results answer the research question? DADT is discussed in the introduction and the discussion, but it is not included in the study question or the materials and methods. Recommend including DADT as part of these sections since it appears to play a major role in the interpretation of the data.</p> <p>Are the interpretation and conclusions warranted by and sufficiently</p>

	<p>derived from/focused on the data? See above comments about DADT.</p> <p>The data only distinguishes between MSM and MSW and leaves out a probable third category - bisexual.</p> <p>The results do match previous findings that this population is at risk for extragenital infections based upon sexual orientation. However, it is difficult to make a conclusion about the first screen effect noted. Theoretically, any individual that has a confirmed HIV diagnosis would have been screened for any STIs that they may be at risk of becoming infected with. There is no data presented to show the difference between first time and subsequent screening in this population. The fact that the mean time of HIV diagnosis was over 5 years for this population makes it hard to state a first screen effect.</p> <p>The manuscript states correctly that a person who recently acquired HIV infection or has a history of STI would be at higher risk for GC/CT, but there is no data to confirm this fact within the study parameters. If the surveys provided greater details such as age, number of partners, initial HIV diagnosis, etc, it could more fully back up the statement.</p>
<b>GENERAL COMMENTS</b>	<p>Strongly recommend putting more emphasis on the DADT and the effects it may have incurred. Inferences are made, but not fully validated.</p> <p>If there is a further breakdown in demographics, recommend showing greater details to help identify a subsection of the population at the greatest risk.</p> <p>Thinking upon the results, this manuscript infers a very high incidence rate of infection, which would naturally lead to ideas about education and prevention. Recommend including the author's recommendations for how to reduce the overall burden amongst the tested population. Such a high rate of infection in this population suggests the need to update or change the screening policies for DoD personnel. It would be useful to state the existing treatment guidelines with proposed changes to improve the overall outcome.</p>

### VERSION 1 – AUTHOR RESPONSE

Regarding Dr. Spaulding's comments, we have added clarification to the introduction. To summarize, all prior studies and reports of GC/CT in the US military, including the Natural History Study, don't include extragenital site data; they include urine or urethra only. Our study is unique in that we did capture extragenital site data and also included a questionnaire of sexual practices and relationship attitudes which has also not been previously collected or reported in US military populations.

Regarding LTC Aldous' comments, we have changed "prevalence" to "incidence", have changed "military men" to "US Navy and Marine Corps men", clarified timing of specimen collection in relationship to survey, and clarified that military GC/CT data that are lacking are extragenital data. We have also included many of the suggested references which were not initially included because they don't include study/report of extragenital GC/CT infection. Those not included weren't included either because we thought they weren't relevant (Switzerland report) or we felt content was already included in another reference. DADT is included in introduction and discussion because we believe it is a major contributor to our results for reasons discussed in manuscript. We did not survey participants about DADT nor do we have a tool to quantify its effect, therefore, it's not mentioned in the materials/methods section. Regarding the "first screen effect", in the introduction, we do mention that extragenital screening was not routinely performed until we designed this study, including in those who are newly diagnosed with HIV infection.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	LTC Wade Aldous, PhD, D(ABMM) Chief, Microbiology Dept of Health Support Services U.S. Army Medical Department Center and School  I have no competing interests.
<b>REVIEW RETURNED</b>	29-Mar-2013

<b>GENERAL COMMENTS</b>	<p>Additional comments made in the attached word document.</p> <p>1. How far back was the time frame to exclude patients? Was it just on the day of the appointment or within 2 months, 6 months, etc? This is a question because one patient was removed from the study for prior treatment, but there is no indication of time frame.</p> <p>2. Is there any data to show that these patients engaging in casual sex had the majority of these infections? Wouldn't this represent the non-caucasian, younger group of patients? The tables note that most of the patients are younger and more recently infected, but no data is listed showing the breakdown of infection by patient grouping. The only breakdown listed is by anatomic site.</p> <p>3. Although many respondents expected monogamy, is there any information about partners and their monogamous status? Just because the patient expects monogamy, unless you can state that their partner was also monogamous, this is just an inference.</p> <p>4. A future study could be performed on females that also participate in anal-oral intercourse. They could potentially have a higher rate of asymptomatic infections, especially since females are generally more asymptomatic than males anyway.</p> <p>5. While this study looked for asymptomatic CT/GC infections in HIV positive males, the incidence of overall infection at specific anatomic sites is incomplete. If an HIV patient came in with complaints of urethritis, were specimens taken from extragenital sites as well? Were there any patients with dual infection? What about presence of other STIs? Both public health officials and the literature currently note an increasing rate of syphilis amongst the young non-caucasian, MSM population. Also, although CT/GC infections can facilitate HIV transmission, the ulcerative diseases (HSV, syphilis, chancroid, LGV, and Donovanosis) will more efficiently facilitate transmission.</p>
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## VERSION 2 – AUTHOR RESPONSE

In response to questions from reviewers:

1. A specific time period was not established in the protocol. The one individual that was excluded was excluded after his provider recalled that he had been recently treated, on the day of his

enrollment in the study.

2. As shown in Table 4, we did not find any significant association between infection and relationship attitudes.

3. No, we did not survey participants about partner specifics beyond gender and condom use.

4. Interesting thought, however, I believe that this sexual practice is primarily limited to MSM. Certainly, women may be at risk for asymptomatic pharyngeal or anal infection from receptive oral or anal sex with men but I wouldn't expect significant risk associated with female oral-anal sex with heterosexual men or women.

5. Generally, yes, if a patient comes to clinic with urethritis and he is MSM, we would test/screen all anatomic sites. This study specifically excluded any symptomatic patient. I'm not sure what is meant by "dual infection"; 81% of our infected participants were positive at 1 anatomic site, 19% at 2 sites, and none at all 3 sites. Study participants underwent comprehensive STI screen and no other STIs were detected in this cohort during the study.

I appreciate the wording change suggestions and have implemented all.