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Asymptomatic Lymphogranuloma Venereum among Nigerian Men who have Sex with Men

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Abstract

Objectives—Recent outbreaks of anorectal lymphogranuloma venereum (LGV) among men who have sex with men (MSM) have been characterised by proctocolitis requiring extended antibiotic treatment as compared to infections caused by other serovars of *Chlamydia trachomatis* (CT). We describe the prevalence and clinical features of LGV among Nigerian MSM diagnosed with anorectal CT.

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COMPETING INTERESTS

TC has received a speaker fee from Gilead Sciences. CG has served as a consultant for BioFire and has received speaker fees from Cepheid and Becton Dickinson. The other authors declare no relevant conflicts of interest.

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AUTHOR CONTRIBUTIONS

Trevor A. Crowell conceptualised these analyses, coordinated data collection, and authored the first draft of the manuscript. Justin Hardick performed LGV testing and assisted in the interpretation of results. Kara Lombardi, Sunday Odeyemi, and Andrew Ivo coordinated and conducted other laboratory testing. Zahra Parker, Afoke Kokogho, Senate Amusu, and Sylvia Adebajo oversaw the collection of clinical data. Stefan D. Baral, Rebecca G. Nowak, Manhattan Charurat, and Julie Ake conceptualised the TRUST/RV368 study and assisted in the interpretation of results from these analyses. Charlotte Gaydos oversaw development of the LGV assay and provided general oversight of these analyses. All authors reviewed this manuscript, provided feedback, and approved of the manuscript in its final form.

Methods—MSM were recruited for this observational cohort in Lagos, Nigeria, using respondent-driven sampling and screened for HIV and bacterial sexually transmitted infections (STIs) every three months for up to 18 months. Nucleic acid amplification tests for CT were performed on rectal swab specimens. Prevalent and incident cases of anorectal CT underwent additional testing to identify LGV utilising novel real-time PCR assays specific for the L-serovars of CT.

Results—From April 2014 to July 2016, 420 MSM underwent testing for rectal STIs, of whom 66 (15.7%) had prevalent anorectal CT. Among those without prevalent disease, 68 developed incident infections during 208 person-years of follow-up. Of 134 prevalent and incident cases of anorectal CT, seven (5.2%) were identified as LGV. None of the seven participants with LGV reported any symptoms. Two of the participants with LGV were simultaneously co-infected with rectal gonorrhoea. HIV co-infection was common among participants with both LGV (n=5, 71%) and non-LGV (n=98, 77%) serovars of CT (p=0.66).

Conclusions—Anorectal LGV was uncommon but present among Nigerian MSM in this study. Consistent screening for L-serovars of CT, or presumptive treatment for LGV in cases with a high suspicion for this diagnosis, could potentially improve patient outcomes and decrease transmission.

Keywords

Chlamydia trachomatis; Lymphogranuloma Venereum; Sexually Transmitted Infection; HIV; Africa; Men Who Have Sex with Men

INTRODUCTION

Lymphogranuloma venereum (LGV) is a sexually-transmitted infection (STI) caused by the L-serovars of *Chlamydia trachomatis* (CT) that has been associated with outbreaks of infectious proctitis and proctocolitis among men who have sex with men (MSM) in Europe and North America.¹ Because of its invasive pathogenesis and long-term sequelae, such as fibrosis and stricture formation, an extended 21-day course of antibiotic therapy is recommended for treatment of LGV as compared to the 7-day course for infections with other CT serovars.² Identification of LGV requires advanced molecular testing that is often unavailable in resource-limited settings such as sub-Saharan Africa.

Nigeria is the most populous country in sub-Saharan Africa and its population accounts for roughly 9% of people living with HIV globally.³ Moreover, stigma and criminalisation of same-sex practices limit STI and LGV case-finding among Nigerian MSM.⁴ We have previously reported prevalence of 44–66% for HIV, 19–26% for gonorrhoea, and 17–18% for CT among MSM in Abuja and Lagos, Nigeria.⁵

In this study, we describe the prevalence and clinical features of LGV among MSM diagnosed with anorectal CT in Lagos, Nigeria.

METHODS

Study Population

The Lagos site of the TRUST/RV368 cohort study enrolled MSM using respondent-driven sampling (RDS) as previously described.⁶⁷ Seven initial “seed” participants and each subsequent enrollee were given three coupons to distribute to other MSM. Eligible participants were 18 years or older, presented a valid RDS coupon, and reported receptive or insertive anal intercourse with a male partner in the preceding 12 months. Participants who enrolled between 28 April 2014 and 19 July 2016 were included in these analyses.

STI Testing and Follow-Up

Participants underwent testing for HIV and other STIs every three months for up to 18 months. Voided urine and self- or physician-collected rectal swabs were tested for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* using the Aptima Combo 2® assay (Hologic, Bedford, MA, USA). Fingerstick blood specimens were screened for HIV infection using a parallel algorithm of two rapid tests with Determine® (Alere, Waltham, MA, USA) and Uni-gold® (Trinity Biotech, Wicklow, Ireland) kits. Testing was conducted according to package inserts. At each visit, medical history, clinical evaluation, STI-related symptoms, and prescribed medications were recorded. Participants were notified of testing results as soon as they were available and were offered immediate treatment of any infection diagnosed.

LGV Assay Design

The polymorphic protein H gene for CT L-serovars (L1, L2, L2b, and L3) was aligned against non-L-serovars using BioEdit (Tom Hall, Raleigh, NC, USA) and ClustalW (European Bioinformatics Institute, Cambridge, UK). Areas unique to the L-serovars were used to design primers and probes (Supplementary Table 1). Limit of detection was determined to be approximately 10 genomic copies/assay. Exclusivity testing was performed using known non-L CT serovars and three near-neighbor species (*C. abortus*, *C. muridarum* and *C. suis*) at multiple concentrations. No cross-reactivity between the L-serovar specific assays was observed.

Testing for LGV Serovars

Anal swabs from participants with prevalent anorectal CT underwent additional testing to identify LGV. Participants without prevalent anorectal CT were followed for incident infection and underwent LGV testing if anorectal CT was diagnosed. Only the first positive specimen for each participant underwent LGV testing.

Nucleic acid extraction was performed using the MagNA Pure LC robot DNA Isolation Kit I (Roche Diagnostics, Indianapolis, IN) as per manufacturer instructions. Amplification reactions were performed as described in Supplementary Table 1.

Statistical Analyses

Characteristics of participants with LGV and non-LGV CT serovars were compared using Fisher’s exact test for categorical variables and Wilcoxon rank-sum test or t-test for

continuous variables. Analyses were performed using Stata 14.2 (Stata Corp LP, College Station, TX, USA).

Ethical Approval

All participants provided written informed consent before enrolment. This study was reviewed and approved by institutional review boards at the Walter Reed Army Institute of Research, Silver Spring, MD, USA; the University of Maryland, Baltimore, MD, USA; and the National Health Research Ethics Committee and Ministry of Defence, Abuja, Nigeria (Approval #FHREC/2012/08//22/09-08-12). The investigators have adhered to the policies for protection of human subjects as prescribed in AR-70.

RESULTS

Study Population

A total of 420 participants (128 HIV-uninfected, 292 HIV-infected) underwent testing for rectal STIs and 66 (15.7%) had prevalent anorectal CT at enrolment. Among those without prevalent disease, 68 developed incident anorectal CT during 208 person-years of observation. A total of 134 first-positive rectal swab specimens with CT underwent LGV identification. Seven (5.2%) cases of infection with LGV serovars were diagnosed.

Participants with anorectal LGV had a median age of 19 years (interquartile range [IQR] 18–26) and participants with non-LGV anorectal CT had a median age of 23 years (IQR 21–26; $p=0.06$).

Symptoms

No participant with anorectal LGV reported symptoms. Among the 127 participants with non-LGV anorectal CT, three (2.4%) reported fever/sweats, two (1.6%) reported rectal pain/sores, two (1.6%) reported abdominal pain and one (0.8%) reported nausea/vomiting.

Co-infections

Five (71.4%) participants with anorectal LGV were HIV-infected, as were 98 (77.2%) with non-LGV anorectal CT ($p=0.66$). Anorectal gonorrhoea was detected in two (28.6%) participants with LGV and 58 (45.7%) with non-LGV anorectal CT ($p=0.46$). Neither urogenital CT nor urogenital gonorrhoea was observed in participants with anorectal LGV. Among participants with non-LGV anorectal CT, these co-infections were found in 13 (10.2%; $p>0.99$) and 10 (7.9%; $p>0.99$), respectively.

Clinical Outcomes

The clinical management and outcomes of participants with LGV are summarised in Table 1. One participant was lost to follow-up before treatment could be administered and one participant received treatment with one week of oral doxycycline but was lost to follow-up before repeat CT testing. All five remaining participants with LGV had documented clearance after therapy. Two participants cleared their infections after self-reported self-administration of antibiotics, which is common practice in Nigeria based on symptoms, exposure, or a positive test. The antibiotics taken were not reported.

DISCUSSION

To our knowledge, this is the first study to identify anorectal LGV infection among MSM in Sub-Saharan Africa. LGV is historically endemic to sub-Saharan Africa but typically associated with ulcerative genital disease.⁸ Few studies have evaluated the anorectal site for infection. One study of 43 HIV-uninfected MSM in Kilifi, Kenya, identified three cases of anorectal CT, but none with LGV.⁹ Healthcare providers should conduct anatomically appropriate screening for STIs based on patients' sexual behaviours and should be aware of the risk of anorectal LGV among MSM.

In contrast to other reports, anorectal LGV was uniformly asymptomatic among Nigerian MSM in this study. In Europe and North America, reports suggest that only 5–27% of cases have been asymptomatic.¹⁰ All cases of LGV in this study would have gone undiagnosed and untreated without universal screening of asymptomatic MSM. While there are financial and logistical barriers to implementation of universal screening, providers should consider additional testing or presumptive therapy for LGV in HIV-infected MSM with anorectal disease or who fail to clear anorectal CT after standard therapy.

In this study, LGV was diagnosed retrospectively and providers prescribed therapy based on CT results only. Still, most infections cleared even without LGV-specific therapy. Limited observational data of mostly symptomatic cases of anorectal LGV suggest that single-dose azithromycin and seven-day courses of doxycycline are less efficacious than a 21-day course of doxycycline, but clinical and microbiologic cure have been observed with these regimens for some individuals.¹ Further research is needed to clarify optimal regimens and duration, particularly in asymptomatic cases.

This study enrolled a highly-marginalised population of MSM in Nigeria and conducted universal screening for anorectal STIs, including LGV, enabling novel characterisation of disease burden in this population. However, this study may have underestimated the burden of symptomatic disease due to factors such as recall bias or selection bias. For example, symptomatic individuals might have been more likely to seek treatment from providers outside of the study or through self-administration of antibiotics. Although STI treatment was available at no cost to participants throughout the study, including outside of regularly scheduled study visits, treatment was frequently delayed or undertaken through self-administration of antibiotics. Data regarding drugs and doses of self-administered antibiotics were not systematically collected. Outcomes of STI treatment were not available for all participants and may have been influenced by factors other than medications prescribed during study participation. Lastly, while the assay used for these analyses identified multiple CT serovars associated with LGV, it did not distinguish between these serovars.

Anorectal LGV was uncommon but present among MSM in Lagos, Nigeria. All cases were asymptomatic and would not have been captured without universal, anatomically-appropriate screening. Syndromic management of anorectal STIs would not have been sufficient to diagnose either LGV or the vast majority of anorectal CT among participants in this study. Furthermore, it is imperative that healthcare providers discuss sexual practices with their patients in order to identify the appropriate anatomic sites to evaluate for STIs,

since infected patients may not present with specific complaints. In Nigeria and other settings where LGV testing is not widely available, healthcare providers may consider presumptive therapy for LGV in cases of anorectal CT that do not respond to the usual therapy. These data suggest that some cases of anorectal LGV can be cured with short courses of antibiotic therapy and further research is needed to define the optimal course of therapy for asymptomatic anorectal LGV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY MESSAGES

- From 2014–2016, seven cases of anorectal LGV were retrospectively detected among 420 Nigerian MSM being screened for sexually transmitted infections.
- HIV co-infection was common among participants with both LGV and infection with non-LGV associated serovars of *Chlamydia trachomatis*.
- All cases of anorectal LGV were asymptomatic at the time of diagnosis.
- Among five LGV cases with re-testing for *Chlamydia* after treatment, all cleared the infection despite therapy other than the extended antibiotic course recommended for LGV.

Characteristics and Management of Participants with Anorectal Lymphogranuloma Venereum

Table 1

ID	Age	Visit Number	HIV	Anorectal Gonorrhoea	Treatment	Outcome
1	18	1	Negative	Negative	Doxycycline 100mg PO BID x 7 days prescribed 120 days after diagnosis	Unknown; LTFU
2	19	1	Negative	Negative	None	Unknown; LTFU
3	18	1	Positive	Positive	Azithromycin 2gm PO x 1 dose prescribed 118 days after diagnosis	Cleared infection at next visit 92 days after treatment
4	19	2	Positive	Positive	Self-prescribed antibiotics	Cleared CT at next visit 101 days after diagnosis, still positive for NG and treated with ceftriaxone 1gm IM x 1 dose
5	18	1	Positive	Negative	Self-prescribed antibiotics	Cleared CT at next visit 237 days after diagnosis, newly positive for NG and treated with ceftriaxone 1gm IM x 1 dose
6	26	1	Positive	Negative	Doxycycline 100mg PO BID x 7 days prescribed 149 days after diagnosis	Cleared infection at next visit 91 days after treatment
7	30	1	Positive	Negative	Doxycycline 100mg PO BID x 7 days prescribed 147 days after diagnosis	Cleared infection at next visit 181 days after treatment

Abbreviations: BID, *bis in die* (two times per day); CT, *Chlamydia trachomatis*; IM, intramuscular; HIV, human immunodeficiency virus; LTFU, lost to follow-up; NG, *Neisseria gonorrhoeae*; PO, *per os* (by mouth). The date of swab collection was used as the diagnosis date for the purpose of calculating days from diagnosis to treatment. Participants were re-tested for STIs at their next scheduled visit after treatment.