Determinants of HIV-1 Load in Subjects with Early and Later HIV Infections, in a General-Population Cohort of Rakai, Uganda

Ronald H. Gray,¹ X. Li,¹ Maria J. Wawer,⁵ David Serwadda,⁶ Nelson K. Sewankambo,⁷ Fred Wabwire-Mangen,⁶ Tom Lutalo,⁸ Noah Kiwanuka,⁸ Godfrey Kigozi,⁸ Fred Nalugoda,⁸ Mary P. Meehan,⁵ Merlin Robb,⁴ and Thomas C. Quinn^{2,3}

¹Department of Population and Family Health Sciences, Bloomberg School of Public Health, and ²Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, ³National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, and ⁴Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, Maryland; ⁵Heilbrun Center for Population and Family Health, Joseph L. Mailman School of Public Health, Columbia University, New York, New York; ⁶Institute of Public Health, and ⁷Department of Medicine and Faculty of Medicine, Makerere University, Kampala, and ⁸Rakai Project, Uganda Virus Research Institute, Entebbe, Uganda

Human immunodeficiency virus (HIV) type 1 RNA loads were determined for 256 subjects with early (incident) HIV infection and for 1293 subjects with later (prevalent) HIV infection, in a Ugandan cohort. Prevalent infections were classified as latent (0–1 symptoms) and midstage disease (≥ 2 symptoms), and deaths were ascribed to acquired immunodeficiency syndrome. Among subjects with incident HIV infection, HIV load did not differ by sex, but, among subjects with prevalent HIV infection, it was higher in males than in females. HIV load was highest in subjects (25–29 years old) with incident HIV infection but increased with age in subjects with prevalent HIV infection. Viremia was higher after serconversion than in latency and increased with more advanced disease. Viremia was increased with genital ulcer disease (GUD) in both subjects with incident infection and in those with prevalent infection, and with herpes simplex virus type 2 seropositivity in subjects with incident HIV infection. GUD was consistently associated with higher HIV loads in subjects with incident and those with prevalent HIV infection, suggesting that treatment of GUD might reduce HIV viremia.

HIV load is an important determinant of heterosexual [1, 2] and mother-to-child transmission of HIV [3, 4], and HIV load early after infection or during the course of disease is predictive of progression and death [5–9]. In many [5, 10–13], but not all, studies [14], HIV loads were found to be higher in men than in women, and concurrent infections with herpes simplex virus type 2 (HSV-2) [15], tuberculosis [16], malaria [17], and helminths [18] have been associated with increased HIV

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viremia. Although the level of viremia during the course of HIV infection has been described for industrialized countries [19, 20], there is relatively little information on the developing world, particularly on sub-Saharan Africa, which is most severely affected by the epidemic and where concurrent bacterial and parasitic infections may alter the natural history and progression of HIV disease. It is, therefore, important to understand the determinants of HIV load in both early (incident) and later (prevalent) HIV infections; therefore, we examined HIV load in adults who provided blood samples during several studies conducted in Rakai District, Uganda.

SUBJECTS, MATERIALS, AND METHODS

We previously conducted a community-based randomized trial of control of sexually transmitted diseases for prevention of AIDS in the rural Rakai District of southwestern Uganda [21]. During surveys conducted at 10month intervals, an average of ~12,000 consenting per-

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Reprints or correspondence: Dr. Ronald H. Gray, Ste. 4030, Johns Hopkins University, School of Hygiene and Public Health, 615 N. Wolfe St., Baltimore, MD 21205 (rgray@jhsph.edu).

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sons were interviewed and asked to provide blood for HIV testing. HIV prevalence was 16.5%, and average annual HIV incidence was 1.5 cases/100 person-years [21]. The study was approved by the Scientific and Ethics Committee of the Uganda Virus Research Institute and by institutional review boards at Columbia and Johns Hopkins Universities.

HIV load was measured in serum samples from 256 subjects with incident HIV infection and on subsamples from subjects with prevalent HIV infection, who were identified during community surveillance between 1994 and 1998. The subsamples from subjects with prevalent HIV infection were as follows: (1) 415 HIV-positive partners in HIV-discordant relationships [1], (2) 326 pregnant and 261 nonpregnant female subjects, 15–49 years old [22], and (3) a random sample of 592 subjects with prevalent HIV infection for the general population. Thus, the sample of subjects with prevalent HIV infection for whom HIV load measurements were available is not fully representative of the total population of subjects with prevalent HIV infection in the Rakai cohort.

HIV RNA was quantified in serum samples by use of reversetranscriptase polymerase chain reaction (RT-PCR), using Amplicor HIV-1 Monitor 1.5 Assay (Roche Molecular Systems), with a lower limit of detection of 400 copies/mL (2.60 log₁₀ copies/mL). The terms "HIV load," "viremia," and "virus burden" are used to designate HIV-1 RNA copies per milliliter of serum. We also assessed HSV-2 serologic status in 562 persons for whom this assay was available (predominantly the subjects with incident HIV infection and HIV-infected partners in the data set of discordant couples). HSV-2 seropositivity was determined by use of HerpSelect 2 ELISA IgG (ELISAs for the detection of human IgG class antibodies to HSV-2; Focus), with confirmation by use of Western blot [23] (performed by R. Ashley, University of Washington, Seattle). HSV-2 seropositivity was defined as a positive result by HerpSelect and Western blot.

For incident HIV infection, the mean time from seroconversion to measurement of HIV load was ~5 months, assuming a uniform distribution of seroconversions during the 10-month follow-up intervals. Thus, the subjects who seroconverted represent an unknown mixture of acute and early incident HIV infections. For descriptive purposes, we will refer to this group as subjects with incident HIV infection or subjects who seroconverted. The duration of infection for subjects with prevalent HIV infection is unknown. At each interview (at 10-month intervals), subjects were asked whether they had symptoms suggestive of AIDS-related illnesses by use of questions on minor and major symptoms, which are components of the World Health Organization (WHO) provisional diagnosis of AIDS [24]. These symptoms included weight loss, chronic diarrhea, cough and fever, generalized pruritic rash, and diagnoses of thrush, herpes zoster, Kaposi sarcoma, and active tuberculosis. Asymptomatic subjects with prevalent HIV infection and those

reporting only 1 symptom were assumed to be in the latent stage of disease, and persons with ≥ 2 symptoms were assumed to be in midstage disease or in early AIDS. Information was also collected on persons who died, and it was assumed that persons who died within 1 year of a determination of HIV load were likely to have had late-stage disease or AIDS. All deceased persons had symptoms compatible with more-advanced disease at the interview before the 10-month interval during which they died, but not all deceased persons met the WHO criteria for AIDS at this interview. This symptom/survival-based classification was used to approximate the stage of HIV disease in subjects with prevalent HIV infection whose duration of infection was unknown. Symptoms of genital ulcer disease (GUD) or genital discharge during the 6 months preceding the interview were also ascertained at each interview. Standardized questions were used to ascertain symptoms of GUD, and persons with current GUD were examined, to verify the reported symptoms, and genital ulcer swabs were collected for testing by multiplex PCR, to detect HSV-2, Treponema pallidum, and Haemophilus ducreyi [21, 26].

We estimated median log₁₀ transformed HIV loads (and 95% confidence intervals [CIs]) and mean log₁₀ HIV loads (and SDs), by age (15–24, 25–29, 30–39, and \geq 40 years), sex, and putative stage of disease (subjects with incident or prevalent HIV infection with 0, 1, 2, or \geq 3 symptoms or those who died), by reports of STD symptoms (GUD or genital discharge), and by HSV-2 serostatus for the subgroup for whom HSV-2 serologic testing results was available. The statistical significance of differences in mean log₁₀ HIV loads between covariate categories was determined by use of t tests. The adjusted HIV load was estimated by use of multivariate linear regression. Variables included in the regression models were those found to be significantly associated with HIV-load differentials in bivariate analyses. Models were also examined for interactions, and adjusted estimates were made by age and stage of disease, incorporating interaction terms. We also assessed nonlinear regression models.

RESULTS

Table 1 shows the HIV loads in the representative population of 256 subjects with incident HIV infection. A high proportion (63.7%) of seroconversions occurred in younger persons (15–29 years old), and the majority (54.7%) of subjects who seroconverted were female. When blood samples were obtained ~5 months after infection, the mean HIV load was 4.38 log₁₀ copies/ mL (median, 4.48 log₁₀ copies/mL) and was slightly higher in males than in females, but this difference was not statistically significant (*P* = .90). Sixty-nine percent of females who seroconverted were <30 years old, compared with 56.9% of males (*P* = .03). HIV viremia was highest among the subjects with incident infection who were 25–29 years old (mean, 4.79 copies/

Table 1.HIV load in subjects who seroconverted, by sex, age,
genital ulcer disease (GUD) status, and herpes simplex virus type
2 (HSV-2) serostatus.

) (NI- (0()	HIV load, mean log ₁₀	D
Variable	No. (%)	copies/mL (SD)	Р
All	256 (100)	4.38 (1.21)	
Male	116 (45.3)	4.39 (1.28)	Referent
Female	140 (54.7)	4.37 (1.15)	.90
Age, years			
15–24	117 (45.7)	4.23 (1.19)	Referent
25–29	46 (18.0)	4.79 (1.10)	.01
30–39	52 (20.3)	4.35 (1.24)	.55
40–59	41 (16.0)	4.38 (1.29)	.48
No GUD	215 (84.0)	4.32 (1.25)	Referent
GUD	41 (16.0)	4.71 (0.91)	.01
HSV-2 seronegative	67 (30.9)	4.06 (1.36)	Referent
HSV-2 seropositive	150 (69.1)	4.56 (1.15)	<.01

mL; median, 4.93 \log_{10} copies/mL), compared with the subjects who were 15–24 or >30 years old (P = .01), and this higher viremia among 25–29-year-olds was observed for both sexes.

Subjects who seroconverted and who reported symptoms of GUD during the interval of HIV acquisition had significantly higher HIV loads than those without symptoms of GUD (mean, 4.71 vs. 4.32 \log_{10} copies/mL; P = .01), and this GUD-associated differential in viremia was observed for both sexes. HSV-2 seropositivity was higher in females (80.0%) than in males (56.9%) (P<.001). HSV-2 seropositivity was also associated with significantly higher HIV viremia in subjects who seroconverted; the mean HIV load in HSV-2-seropositive subjects was 4.56 log₁₀ copies/mL, compared with 4.06 log₁₀ copies/mL in HSV-2seronegative subjects (P < .01). The increase in HIV load was observed in 28 HSV-2-seropositive subjects with symptoms of GUD (4.64 log₁₀ copies/mL), 122 HSV-2-seropositive subjects without symptoms of GUD (4.53 log₁₀ copies/mL), and 9 HSV-2-seronegative persons with symptoms of GUD (4.81 copies/ mL), but viremia was lower in 58 HSV-2-seronegative persons without symptoms of GUD (3.94 log₁₀ copies/mL). Thus, the increased HIV load was independently associated with both symptoms of GUD and HSV-2 seropositivity. Analyses stratified by sex showed no statistically significant differences in HIV loads between male and female subjects with incident HIV infection, for any covariates, although small numbers within sex-specific subgroups limited the power of the analysis (data not shown.) Symptoms of genital discharge were not associated with variation in HIV loads (data not shown).

Table 2 shows comparable data for the 1293 subjects with prevalent HIV infection. It must be reiterated that this was not a representative random sample of all subjects with prevalent HIV infection in the Rakai population, because data were derived from selected substudies with available HIV load mea-

surements. In particular, females were overrepresented (68.8%), relative to males (31.2%), and the subsample of females was younger than the subsample of males (<30 years old, 66.9% vs. 37.1%; P < .001). The overall HIV load in males with prevalent HIV infection (mean, 4.46 log₁₀ copies/mL; median, 4.45 log₁₀ copies/mL) was significantly higher than that in females with prevalent HIV infection (mean, 4.25 log₁₀ copies/mL; median, 4.29 log₁₀ copies/mL; P<.001). HIV load increased significantly with age, from a mean of 4.22 log₁₀ copies/mL in persons 15-24 years old to a mean of 4.58 log₁₀ copies/mL in persons 40–59 years old (P < .001). This trend of increasing HIV load with older age was observed in both males (P = .03) and females (P = .03). HIV loads in males were higher than those in females, within each age group, but there were no statistically significant age-specific differences in virus burden between sexes, with the exception of the subjects who were 30-39 years old, in which males had significantly higher HIV loads than females (mean, 4.49 vs. 4.25 \log_{10} copies/mL, respectively; P = .01).

The majority (56.5%) of subjects with prevalent HIV infection were asymptomatic, and this was similar in males (54.2%) and in females (57.5%). However, a significantly higher proportion of males had more-advanced disease, as indicated by persons reporting \geq 3 symptoms or persons who died (17.5% of males vs. 11.0% of females; *P* = .003). HIV load increased significantly with more-advanced disease, and this trend was

 Table 2.
 HIV load in subjects with prevalent HIV infection, by age, symptomatology, genital ulcer disease (GUD) status, and herpes simplex virus type 2 (HSV-2) serostatus.

	HIV load, mean \log_{10}	_
No. (%)	copies/mL (SD)	Р
1293 (100)	4.31 (0.92)	
404 (31.2)	4.46 (0.56)	Referent
889 (68.8)	4.25 (0.90)	.0002
409 (31.6)	4.22 (0.91)	Referent
336 (26.0)	4.25 (0.95)	.70
393 (30.4)	4.36 (0.92)	.04
155 (12.0)	4.58 (0.86)	.001
730 (56.5)	4.23 (0.92)	Referent
305 (23.6)	4.18 (0.87)	.40
89 (6.9)	4.50 (0.96)	.01
47 (3.6)	4.58 (0.80)	.01
122 (9.4)	4.89 (0.84) ^a	< .001
1097 (84.8)	4.27 (0.93)	Referent
196 (15.2)	4.59 (0.87)	< .001
115 (33.3)	4.18 (0.84)	Referent
230 (66.7)	4.09 (0.83)	.39
	404 (31.2) 889 (68.8) 409 (31.6) 336 (26.0) 393 (30.4) 155 (12.0) 730 (56.5) 305 (23.6) 89 (6.9) 47 (3.6) 122 (9.4) 1097 (84.8) 196 (15.2) 115 (33.3)	No. (%) copies/mL (SD) 1293 (100) 4.31 (0.92) 404 (31.2) 4.46 (0.56) 889 (68.8) 4.25 (0.90) 409 (31.6) 4.22 (0.91) 336 (26.0) 4.25 (0.95) 393 (30.4) 4.36 (0.92) 155 (12.0) 4.58 (0.86) 730 (56.5) 4.23 (0.92) 305 (23.6) 4.18 (0.87) 89 (6.9) 4.50 (0.96) 47 (3.6) 4.58 (0.80) 122 (9.4) 4.89 (0.84) ^a 1097 (84.8) 4.27 (0.93) 196 (15.2) 4.59 (0.87) 115 (33.3) 4.18 (0.84)

^a P = .0001, test for linear trend with age and stage of disease.

^b Subgroup for whom HSV-2 serologic testing results were available.

	Subjects who seroconverted		Subjects with prevalent HIV infection	
Variable	Coefficient (SE)	Р	Coefficient (SE)	Р
Constant	4.118 (0.134)	<.00001	4.134 (0.051)	<.0001
Sex (male, female referent)	0.022 (0.151)	.89	0.138 (0.057)	.016
Age, years				
15–24	Referent		Referent	
25–29	0.603 (0.208)	.004	-0.025 (0.067)	.71
30–39	0.157 (0.201)	.43	0.044 (0.066)	.51
≥40	0.233 (0.220)	.29	0.211 (0.089)	.018
Stage of disease				
Asymptomatic	NA		Referent	
1 symptom	NA		-0.041 (0.061)	.50
2–3 symptoms	NA		0.211 (0.085)	.013
Death	NA		0.582 (0.089)	<.001
No GUD	Referent		Referent	
GUD Present	0.454 (0.206)	.03	0.249 (0.071)	<.0001
HSV-2 seronegative	Referent		NA	
HSV-2 seropositive	0.442 (0.195)	.03	NA	

Table 3. Multivariate adjusted \log_{10} HIV load for subjects with incident and prevalent HIV infection.

NOTE. NA, not available.

highly significant (P = .001). Compared with asymptomatic subjects with prevalent HIV infection (mean HIV load, 4.23 log₁₀ copies/mL), viremia was significantly and substantially increased in those with 2 symptoms (mean, 4.50 log₁₀ copies/mL; P = .01) or ≥ 3 symptoms (mean, 4.58 log₁₀ copies/mL; P = .01) or in persons who died (mean, 4.89 log₁₀ copies/mL; P < .001). Similar statistically significant increases of HIV load, with moreadvanced disease, were observed in both males and females (data not shown). Asymptomatic males had significantly higher HIV loads than did females (mean, 4.39 vs. 4.17 log₁₀ copies/mL; P = .003), but no significant sex-specific differences were observed in HIV loads among symptomatic persons or those who died of AIDS.

Subjects with prevalent HIV infection who reported symptoms of GUD had higher HIV loads than did those without symptoms of GUD (mean, 4.59 vs. 4.27 \log_{10} copies/mL; *P* = .001), and this differential was observed both in males (*P* = .007) and in females (*P* = .001). HSV-2 seropositivity was more common in female (74.3%) than in male (59.6%) subjects with prevalent HIV infection (*P* = .005), but, overall, there were no significant differences (*P* = .39) in HIV load between HSV-2–seropositive subjects with prevalent HIV infection and HSV-2–negative subjects with prevalent HIV infection, or between sexes. Symptoms of genital discharge had no effect on HIV load (results not shown).

As noted above, male subjects with prevalent HIV infection had higher HIV loads than females, but these unadjusted dif-

ferentials could reflect confounding by age and stage of disease. Therefore, multivariate linear regression was used to estimate adjusted HIV loads. Table 3 shows the coefficients from the multivariate models, for subjects who seroconverted and for subjects with prevalent HIV infection. The adjusted log₁₀ HIV load for each covariate can be estimated from the sum of the coefficient of the constant plus the coefficient for the covariate of interest. For example, among subjects with prevalent HIV infection, males had a significantly higher HIV load than females (adjusted HIV load, $4.134 + 0.138 = 4.27 \log_{10}$ copies/ mL for males vs. 4.13 \log_{10} copies/mL for females; P = .016). Among subjects with incident HIV infection, there was no significant difference in HIV load by sex. The adjusted HIV loads were significantly higher in the subjects with incident HIV infection who were 25–29 years old (P = .004), but, among subjects with prevalent HIV infection, HIV load was highest in older persons (40–49 years old; P = .018). The increase in HIV load with more-advanced disease among subjects with prevalent HIV infection persisted after adjustment and was significant for those reporting ≥ 2 symptoms (P = .013) and for those who died (P < .001). GUD was associated with significantly higher adjusted viremia in both subjects with incident HIV infection (P = .03) and those with prevalent HIV infection (P < .001). HSV-2 was associated with higher adjusted viremia in subjects with incident HIV infection (P = .03), but not in subjects with prevalent HIV infection.

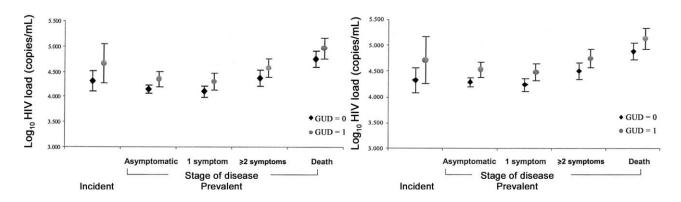


Figure 1. Model adjusted mean HIV loads and 95% confidence intervals, for subjects with early (incident) and for those with later (prevalent) HIV infection, by stage of disease and by the presence (genital ulcer disease [GUD] = 1) or absence (GUD = 0) of symptomatic GUD, in subjects 15–29 years old (*left*) and 30–59 years old (*right*).

CIs for subjects with incident HIV infection and for subjects with prevalent HIV infection, by stage of disease, among subjects with and without reported symptoms of GUD, stratified into 2 age groups, 15–29 and 30–59 years. There was an increased viremia after seroconversion, with an apparent decrease to set point among subjects with prevalent HIV infection who were asymptomatic or who reported only 1 symptom, and there was a subsequent increase in virus burden among subjects with prevalent HIV infection in late-stage disease. In both younger and older persons, GUD was associated with higher viremia at all stages of disease.

DISCUSSION

These cross-sectional observational data from a general-population cohort in rural Uganda suggest that cofactors influencing HIV load differ between incident and prevalent HIV infections. For example, among subjects with incident HIV infection, there were no significant differences in viremia by sex (table 1), whereas, among subjects with prevalent HIV infection, males had significantly higher HIV loads than females, even after adjustment for other covariates (tables 2 and 3). Among subjects with incident HIV infection, viremia was highest in persons 25–29 years old, whereas, among subjects with prevalent HIV infection, viremia increased progressively with age. Also, HSV-2 seropositivity was associated with higher viremia in subjects with incident, but not prevalent, HIV infection (tables 1 and 2).

Our findings of higher HIV loads in male subjects with prevalent HIV infection than in female subjects with prevalent HIV infection is consistent with findings of studies in the United States and Europe [5, 10–13]. However, the finding of small and nonsignificant sex-associated differentials in HIV load among subjects with incident HIV infection acquired by heterosexual transmission in the present Ugandan study differs from the finding that, among intravenous drug users (IDUs) with incident HIV infection, males have higher HIV loads than females [5, 9, 11]. Therefore, the mode of infection may affect sex-associated differentials in viremia, but, given that, in the present study, the interval between HIV infection and the first postseroconversion blood sample is unknown and may be as long as 10 months, no conclusions can be drawn.

The HIV load in subjects with incident HIV infection was substantially higher among persons 25-29 years old at time of acquisition, compared with other age groups (table 1 and 3), whereas age was not found to affect postseroconversion viremia in US and European studies of IDUs, MSMs, or patients with hemophilia [5, 9, 25]. Thus, age at infection may affect postseroconversion viremia after vaginal intercourse but may not be associated with viremia after parental or anal transmission, in which the infectious dose is likely to be higher. The US and European subjects who seroconverted were older than the Rakai subjects with incident HIV infection, and this may have obscured age associations in the former populations. Among subjects with prevalent HIV infection, viremia increased with older age and with more-advanced disease, as has been reported by other investigators [9]. Our findings that viremia was higher in subjects with incident infection after seroconversion, compared with that in asymptomatic subjects with prevalent HIV infection, and that HIV load increased with more-advanced disease are comparable to findings from studies in the United States [5, 8, 11] and other developing countries [26].

The findings that HIV load was consistently and significantly higher among persons who reported symptoms of GUD (tables 1 and 2) and that symptoms of GUD remained a significant predictor of viremia in adjusted analyses (table 3) are noteworthy and have not been reported previously. HSV-2 seropositivity was also associated with higher HIV viremia in subjects with incident HIV infection (table 1), but not in subjects with prevalent HIV infection. Prior studies in Rakai have shown that HSV-2 is the predominant cause of GUD in this population [21, 26], and it is likely that most reported cases of GUD are of herpetic origin. Other studies have found that active herpes is associated with higher HIV load and that suppression of HSV-2 by use of acyclovir reduced the HIV load [15]. It is thought that active herpes may up-regulate replication of HIV [15]. In addition, other studies have shown that HSV-2 seropositivity and symptoms of GUD are associated with acquisition of HIV [27, 28]. Thus, the consistent finding of higher viremia in persons with GUD and the likelihood that most GUD is of herpetic origin suggests that screening for HSV-2 and treatment of GUD may be of potential utility in reducing both HIV load in infected persons and the risks of transmission of HIV to uninfected partners.

The present observational study has limitations. The subjects with prevalent HIV infection were not a random sample, but were dictated by the availability of virus-load assays conducted for other investigations. Thus, the findings may not be fully representative of all subjects with prevalent HIV infection in the Rakai population. Nevertheless, analyses of the 586 randomly selected subjects with prevalent HIV infection (data not shown) demonstrated associations between covariates and HIV burden that were similar to those observed in the total sample of subjects with prevalent HIV infection, which suggests that any bias is likely to be minimal. We have found that pregnant females have lower HIV loads than nonpregnant females [22], but exclusion of pregnant females from the analysis did not materially affect our findings. Serum HIV-1 RNA levels are lower than those in plasma and may differ by ~20%–27% [29]. Thus, we cannot make direct comparisons of HIV loads between the serum-based assays used in the present study and the plasma virus burdens reported in other studies. However, this should not affect the observed differentials in viremia (e.g., by sex, age, stage of disease, or GUD status) in the present study. In the present home-based study, quality control of sample collection is probably better with serum than with plasma in a field setting. Similarly, CD4 cell counts were not available for the majority of these subjects, because home-based sample collection limited our ability to collect fresh blood samples; therefore, immune status could not be evaluated.

In conclusion, since HIV load is associated with progression of disease and the likelihood of transmission of HIV, cofactors such as GUD status and HSV-2 seropositivity, which are associated with a higher HIV burden, may be of public health importance to HIV epidemic dynamics in sub-Saharan Africa. Our findings suggests that consideration should be given to screening for HSV-2 and treatment of GUD in HIV-positive persons, because this could be beneficial to HIV-infected individuals and, potentially, might decrease the risk of transmission of HIV.

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