Herpes simplex virus type 2 (HSV-2), the principal cause of genital herpes, infects the majority of human immunodeficiency virus type 1 (HIV-1)–infected persons worldwide [1]. HIV-1 is shed at high titers in genital ulcers caused by HSV-2 [2], and genital ulcer disease (GUD) increases the risk of HIV-1 transmission [3]. Asymptomatic HSV-2 reactivation (ie, viral shedding in the absence of genital lesions) occurs commonly in persons with HIV-1 infection [4], and symptomatic and asymptomatic HSV-2 reactivations have been associated with increased HIV-1 concentrations in plasma and genital secretions [5]. Together, these results suggest that HSV-2 reactivation, both with and without GUD, heightens the infectiousness of individuals with HSV-2 and HIV-1 dual infection.

Acyclovir and its prodrug valacyclovir are routinely and safely used as episodic and daily suppressive treatment against symptomatic GUD due to HSV-2, and suppressive therapy also substantially decreases asymptomatic genital HSV-2 shedding [6]. Five short-term, randomized trials among persons with HIV-1 and HSV-2 dual infection who were not receiving antiretroviral therapy found that daily HSV-2 suppressive therapy for 8–12 weeks with acyclovir or valacyclovir reduced plasma HIV-1 levels by 0.25–0.5 log_{10} copies/mL and also reduced HIV-1 concentrations in endocervical, rectal, and semen samples [7–12]. These proof-of-concept studies suggest that HSV-2 suppressive therapy could be a long-term intervention to reduce HIV-1 transmission risk.

In this issue of the Journal, Tanton et al [13] report the results of a long-term randomized trial of acyclovir suppressive therapy among women from Tanzania with dual HSV-2 and HIV-1 infection. The trial was a considerable undertaking. Nearly 500 women were randomized to daily acyclovir or placebo, seen quarterly, and followed-up for up to 24 months. In contrast with the results of the previous short-term studies, acyclovir did not significantly reduce plasma and genital HIV-1 levels when measured at 6, 12, and 24 months after initiation of suppressive therapy. These results are surprising and disappointing, given the consistency of the previous observational and placebo-controlled interventional studies that have demonstrated a strong relationship between HSV-2 reactivation and systemic and genital HIV-1 levels, and they suggest that acyclovir HSV-2 suppression is unlikely to be an effective long-term strategy to reduce HIV-1 infectiousness. Several possible factors may explain the failure of acyclovir to reduce systemic and genital HIV-1 levels in the trial reported by Tanton et al [13], including the dosage of HSV-2 suppressive therapy, the development of viral resistance, and suboptimal study drug adherence.

An HSV-2 suppressive regimen of acyclovir administered at 400 mg orally twice daily was chosen for the study reported in this issue [13]. One possible explanation for that study’s findings may be that this dosage was insufficiently potent to suppress HSV-2 reactivation and cause a reduction in HIV-1 replication. Although a higher dosage of acyclovir or valacyclovir (which achieves higher plasma concentrations than acyclovir) could have been used, it is unlikely that dosage alone explains the trial results. Previous studies among persons with HSV-2 and HIV-1 dual infection have shown comparable effects in reducing HSV-2 reactivation for daily acyclovir and valacyclovir [6]. Moreover, in contrast to the Tanzania results, another recently completed randomized, placebo-controlled, multicenter trial (the Partners in Prevention HSV/HIV Transmission Study, on which I am a co-investigator) found that the identical regimen of acyclovir (400 mg twice daily) reduced plasma HIV-1 levels by 0.25 log_{10} copies/mL among >3300 African men and women with HSV-2 and HIV-1 dual infection throughout 24 months of follow-up [14]. Notably, in the Partners in Prevention HSV/HIV Transmission Study,
there was no statistically significant reduction in HIV-1 transmission to the sexual partners of those randomized to acyclovir, compared with those randomized to placebo, which provided a direct determination that an average 0.25 log_{10} copies/mL reduction in systemic HIV-1 replication by acyclovir was insufficient to reduce HIV-1 infectiousness. Whether higher dosages of acyclovir or valacyclovir might have greater effects on reducing HIV-1 levels (and HIV-1 infectivity) is an important topic for additional research.

Development of viral resistance, either in HSV-2 or in HIV-1, could also explain the lack of a long-term effect of acyclovir on HIV-1 replication seen in the Tanzania study. HSV-2 resistance to acyclovir rarely develops, even in persons with HIV-1 infection [1], and thus HSV-2 resistance is unlikely to have been an important contributor to the study findings. Acyclovir has not usually been considered to promote HIV-1 resistance. However, recent in vitro studies have found that acyclovir inhibits HIV-1 reverse transcriptase and could thereby act directly to reduce HIV-1 replication by a mechanism separate from an anti-HSV-2 pathway [15–17]. In one study, acyclovir exposure over a period of >90 days resulted in evolution of a specific HIV-1 reverse transcriptase mutation (V75I) that conferred subsequent HIV-1 resistance to acyclovir’s effects [15]. Whether acyclovir selects similar HIV-1 reverse transcriptase resistance in vivo is unknown and requires study. Still, the Partners in Prevention HSV/HIV Transmission Study data suggest that standard doses of acyclovir do not result in loss of an acyclovir effect on plasma HIV-1 levels over 24 months of exposure [14], arguing that HIV-1 resistance may not explain the Tanzania results.

Suboptimal adherence to the acyclovir study regimen is likely the principal explanation for the lack of effect of acyclovir on plasma and genital HIV-1 levels in the trial reported in this issue [13]. Just over 50% of study participants had ≥90% study drug adherence (median overall adherence, 91%), as estimated from pill counts of bottles returned at study visits. However, biological data suggest that this adherence measure is an overestimate. Daily HSV-2 suppressive therapy reduces asymptomatic genital HSV-2 reactivation in HIV-1–infected persons [6, 18], yet there was no statistically significant difference in genital HSV detection by polymerase chain reaction at 6, 12, and 24 months between those randomized to acyclovir and those randomized to placebo. Among participants who had estimated study drug adherence ≥90%, there was a suggestion of greater genital HSV suppression by acyclovir (odds ratio for HSV detection, 0.60; P = .09), but this 40% reduction in detection is considerably less than the >80% reduction seen in previous studies of daily HSV-2 suppression [7, 8]. Genital HSV-2 detection is a strong surrogate measure for adherence to daily anti–HSV-2 therapy (and theoretically an intermediate step for the effect of acyclovir on reducing HIV-1 replication), and the lack of a substantial reduction in HSV-2 reactivation in the acyclovir arm argues that overall adherence in the study population was suboptimal. The relatively low-dosage acyclovir regimen used may have required high and sustained adherence to demonstrate benefit, given the short plasma half-life of acyclovir.

Although the importance of adherence to successful HIV-1 treatment is well-established, considerably less attention has been given to understanding adherence to HIV-1 prevention interventions. Many biomedical prevention strategies that are currently under investigation—for example, antiretroviral preexposure prophylaxis and topical vaginal microbicides—are testing daily or coitally dependent use of study products. Suboptimal adherence has been seen in HIV-1 prevention trials of the vaginal diaphragm and vaginal microbicides [19, 20]. For a trial that does not demonstrate efficacy for preventing HIV-1 infection, low adherence may make it impossible to differentiate whether the intervention itself was ineffective or whether low adherence essentially resulted in nonassessment of the intervention. Notably, the most striking clinical trial success for prevention of sexual HIV-1 transmission in recent years—circumcision to reduce HIV-1 acquisition risk in men [21–23]—is a one-time intervention that requires no sustained adherence.

In the Tanzania trial [13], adherence promotion was performed throughout the study period: by clinic staff at study visits every 3 months and by mobile adherence support teams between study visits. Despite these efforts, adherence in the high-risk, mobile, and socially marginalized population of female bar workers in which the trial was conducted may have been insufficient to optimally evaluate the effect of acyclovir on HIV-1 replication. Some might argue that low adherence in an HIV-1 prevention trial is itself an indication that an intervention is unlikely to be successful if implemented (ie, if trial participants are not using the product, then it is unlikely to be taken up in the “real world”). However, use of an investigational agent in a clinical trial setting (with participants who are motivated but who also have knowledge that the intervention is unproven and may be a placebo) does not necessarily predict future use of a product that demonstrates strong efficacy for the prevention of HIV-1 infection. HIV-1 prevention trials are time- and resource-intensive, and maximizing product adherence is as critical to trial success as other measures of trial conduct, such as recruitment and retention. The standard measures for adherence assessment, including self-report of product use and clinic-based counts of unused product, are susceptible to social desirability bias in the context of ongoing study clinic visits. Thus, accurate and objective measures of adherence, such as biomarkers (eg, blood or tissue levels of a study agent) or confirmatory measures of product use (eg, unannounced counts of study pills between clinic visits [24]),
should be developed for HIV-1 prevention trials.

Acyclovir, at least at a dosage of 400 mg orally twice daily, does not significantly reduce HIV-1 transmission risk. Ongoing small studies will assess whether higher dosages and different agents for HSV-2 suppression might be useful for decreasing HIV-1 replication in persons with HSV-2 and HIV-1 dual infection. Maximizing adherence is critical to the evaluation of novel interventions under study in HIV-1 prevention trials.

References