Daily aciclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial


Summary
Background Most people infected with HIV-1 are dually infected with herpes simplex virus type 2. Daily suppression of this herpes virus reduces plasma HIV-1 concentrations, but whether it delays HIV-1 disease progression is unknown. We investigated the effect of aciclovir on HIV-1 progression.

Methods In a trial with 14 sites in southern Africa and east Africa, 3381 heterosexual people who were dually infected with herpes simplex virus type 2 and HIV-1 were randomly assigned in a 1:1 ratio to aciclovir 400 mg orally twice daily or placebo, and were followed up for up to 24 months. Eligible participants had CD4 cell counts of 250 cells per μL or higher and were not taking antiretroviral therapy. We used block randomisation, and patients and investigators were masked to treatment allocation. Effect of aciclovir on HIV-1 disease progression was defined by a primary composite endpoint of first occurrence of CD4 cell counts of fewer than 200 cells per μL, antiretroviral therapy initiation, or non-trauma related death. As an exploratory analysis, we assessed the endpoint of CD4 falling to <350 cells per μL. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00194519.

Findings At enrolment, the median CD4 cell count was 462 cells per μL and median HIV-1 plasma RNA was 4-1 log₁₀ copies per μL. Aciclovir reduced risk of HIV-1 disease progression by 16%; 284 participants assigned aciclovir versus 324 assigned placebo reached the primary endpoint (hazard ratio [HR] 0.84, 95% CI 0.71–0.98, p=0.03). In those with CD4 counts ≥350 cells per μL, aciclovir delayed risk of CD4 cell counts falling to <350 cells per μL by 19% (0.81, 0.71–0.93, p=0.002).

Interpretation The role of suppression of herpes simplex virus type 2 in reduction of HIV-1 disease progression before initiation of antiretroviral therapy warrants consideration.

Funding Bill & Melinda Gates Foundation.

Introduction
Recent expansion of access to antiretroviral therapy has had a large effect on disease progression and mortality of people with HIV-1 infection in resource-poor countries. However, only a third of people with HIV-1 who meet international antiretroviral therapy initiation guidelines are given these drugs.¹ The number of people needing antiretroviral therapy will continue to grow, despite constraints on antiretroviral programmes and resources—especially if increased CD4 thresholds are adopted for initiation of antiretroviral therapy (eg, 350 cells per μL). Moreover, most people infected with HIV-1 worldwide have counts that are higher than the therapy starting thresholds of 200 or 350 CD4 cells per μL. Thus, low-cost interventions to slow HIV-1 disease progression are needed for those who do not meet present antiretroviral initiation guidelines.

Infection with herpes simplex virus type 2 is the most common cause of genital ulcer disease worldwide. Seroprevalence of this virus in people with HIV-1 ranges from 70% to more than 90%.² Reactivation of this herpes virus is common and often asymptomatic in HIV-1-infected people, occurring on about a third of days.³ Plasma and genital HIV-1 concentrations increase during reactivation,⁴ suggesting that herpes reactivation enhances HIV-1 replication, possibly through binding of herpes simplex virus proteins to the HIV-1 long-terminal repeat, raising concentrations of pro-inflammatory cytokines, or through infiltration of HIV-1 target cells in the genital tract.⁵⁻⁷

In view of the strong relation between raised plasma HIV-1 concentrations and increased speed of HIV-1 disease progression,⁸⁻¹⁰ suppression of herpes virus type 2 has been regarded as a potential strategy to reduce HIV-1 concentrations and slow its progression. Researchers of five randomised trials¹¹⁻¹⁶ of people dually infected with these viruses who were not taking antiretroviral therapy reported that daily herpes suppressive therapy with aciclovir or valaciclovir for 8–12 weeks reduced plasma HIV-1 concentrations by 0.25–0.5 log₁₀ copies per μL.¹¹⁻¹₆
We undertook a multicentre trial of daily suppression of herpes simplex virus type 2 with aciclovir in Africans who were dually infected with HIV-1 and herpes simplex virus type 2 to assess the efficacy of suppressive aciclovir on measures of HIV-1 disease progression.

Methods

Participants

Heterosexual couples who were discordant for HIV-1 infection were recruited at sites in southern Africa (Gaborone Botswana; Cape Town, Orange Farm, and Soweto South Africa; and Kitwe, Lusaka, and Ndola Zambia) and east Africa (Eldoret, Kisumu, Nairobi, and Thika, Kenya; Kigali Rwanda; Moshi Tanzania; and Kampala Uganda) between Nov 23, 2004 and May 16, 2007. Eligible HIV-1 infected partners were 18 years or older, seropositive for HIV-1 and herpes simplex virus type 2, and had a CD4 cell count of 250 cells per μL or higher. We excluded those who, at enrolment, had an AIDS-defining diagnosis, reported taking antiretroviral therapy, had previous adverse reactions to aciclovir or planned use of antivirals, or were pregnant. The University of Washington Human Subjects Review Committee and ethical review committees at each local institution, collaborating organisation, and national regulatory board approved the study protocol. All participants provided written informed consent.

Procedures

The Partners in Prevention HSV/HIV Transmission Study was a randomised, double-blind, placebo-controlled trial of twice daily aciclovir 400 mg for herpes simplex virus type 2 suppression, given to the partner with dual HIV-1 and herpes type 2 infection within heterosexual HIV-1 serodiscordant couples (ie, one partner was HIV-1 infected and the other was not). The primary aim of the trial was to measure efficacy of aciclovir on reduction of HIV-1 transmission. As reported elsewhere, aciclovir did not reduce HIV-1 transmission within couples, despite reduction of herpes virus type-2-positive genital ulcer disease by 73% and HIV-1 plasma concentrations by 0·25 log₉ copies per μL. Study procedures have been described elsewhere. After the trial was underway, investigators identified that the number of clinical events related to HIV-1 disease (eg, CD4 cell count falling to <200 cells per μL and initiation of antiretroviral therapy) was sufficient to warrant an analysis of HIV-1 disease progression by study group. The Data and Safety Monitoring Board accepted an addendum to the statistical analysis plan describing this analysis.

Participants were followed up every month for up to 24 months after enrolment. At each visit, a 1-month supply of study drug and adherence counselling was provided. Adherence to study drug was assessed by pill count and self-report, defined as 100% adherence or less than 100%. Women were tested for pregnancy every 3 months and when they reported missed menses. Those who became pregnant had their study drug interrupted for the duration of pregnancy, and were referred to local antenatal clinics for prevention of mother-to-child transmission (PMTCT) services. CD4 cell counts were measured twice per year and clinical assessment was undertaken every 3 months. Participants meeting national CD4 cell count and clinical criteria for antiretroviral therapy initiation during follow-up were offered this therapy through referral to local clinics or at the study site. Cause of death of participants who died during follow-up was obtained from family members and medical records, when available. Participants received intensive risk-reduction counselling (both individually and as a couple), free condoms, and treatment of sexually transmitted infections at enrolment and during follow-up visits. Follow-up was continued for participants who reached an HIV-1 disease-progression endpoint.

Figure 1: Trial profile

HSV2=herpes simplex virus type 2. ART=antiretroviral therapy. *HSV2 seropositivity at enrolment confirmed by western blot (WB). †Numerator includes attended visits only. Denominator includes all expected visits including staged site close-out. During follow-up, three participants were dispensed with a drug kit for the incorrect randomisation group, follow-up time has been censored at the visit when this occurred.
Randomisation and masking

The randomisation method was developed and implemented by the study statistician, JPH, and used block sizes of 4, 6, 8, and 10, stratified by site. We used the randomisation list to assemble sequentially numbered, identical sealed kits containing, in a 1:1 ratio, sufficient aciclovir (400 mg, orally, twice daily) or matched placebo (Ranbaxy Laboratories, Haryana, India) for the entire study period. At enrolment, HIV-1-infected partners were assigned the next sequentially numbered kit. Participants were instructed to take one tablet in the morning and one in the evening, and to double the next dose if a dose was missed. Investigators (apart from an unmasked statistician and two data managers from the coordinating centre) remained masked to randomisation assignments throughout the study follow-up.

Study endpoints

Three measures to assess the effect of aciclovir on HIV-1 disease progression were identified before study unblinding: (1) CD4 cell counts falling to fewer than 200 cells per μL, (2) first reported use of antiretroviral therapy (excluding antiretrovirals used for PMTCT), and (3) death from non-trauma causes. The primary analysis was a composite endpoint defined as the first occurrence of any of these three outcomes; only the first HIV-1 disease-progression endpoint was included in the primary composite endpoint if a participant had more than one (eg, CD4 cell count falling to fewer than 200 cells per μL after antiretroviral therapy was initiated).

Statistical analysis

For statistical analyses, we used SAS 9.2. All analyses were by intention to treat. We used Cox proportional hazards regression models, stratified by site, to compare time to occurrence of HIV-1 disease progression outcomes between the two intervention groups, and applied the Efron method for handling ties.29 We used the Kaplan-Meier method to estimate and plot by intervention group the cumulative probability of reaching the study endpoint. Additionally, we undertook Cox proportional hazards analyses for the composite disease-progression endpoint for prespecified subgroups that were defined by the following baseline characteristics: sex, HIV-1 plasma-viral load, and CD4 cell count. Tests for differential treatment effects across subgroups were based on likelihood ratio comparisons between models with and without appropriate interaction terms.

We calculated adherence to study drug as the product of the proportion of dispensed drug taken and the proportion of visits at which the drug was dispensed. Among 95.1% of study visits for which the proportion of dispensed drug taken could be ascertained, 99.2% were established by pill count from returned study drug bottles; in the remaining 0.8% of visits that did not have pill counts but in which participants self-reported adherence, the proportion of study drug taken was

As previously described,20,29 serological tests for HIV-1 were by dual rapid tests with confirmatory EIA, and for herpes simplex virus type 2 were by HerpeSelect-2 EIA (Focus Technologies, Cypress, CA, USA), with an index value of 3·5 or higher to improve test specificity.20–24 Serostatus for both infections was confirmed in batched testing at the University of Washington by western blot with enrolment sera, with people who were not confirmed by western blot excluded from analysis.28 CD4 testing was undertaken at study sites with standard flow cytometry (BD Biosciences, San Jose, CA, USA).

### Table 1: Enrolment characteristics by study group

<table>
<thead>
<tr>
<th></th>
<th>Women (n=2284)</th>
<th>Men (n=1097)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aciclovir (n=1132)</td>
<td>Placebo (n=1152)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29 (25–34)</td>
<td>29 (25–34)</td>
</tr>
<tr>
<td>CD4 cells per μL</td>
<td>484 (369–674)</td>
<td>480 (349–655)</td>
</tr>
<tr>
<td>HIV-1 plasma RNA log10 copies per μL</td>
<td>4.0 (3.2–4.6)</td>
<td>3.9 (3.2–4.5)</td>
</tr>
<tr>
<td>HIV-1-associated symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss &gt;10%*</td>
<td>57 (5%)</td>
<td>47 (4%)</td>
</tr>
<tr>
<td>Fever for more than 1 month*</td>
<td>34 (3%)</td>
<td>38 (3%)</td>
</tr>
<tr>
<td>Diarrhoea for more than 1 month*</td>
<td>7 (1%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Cough for more than 1 month*</td>
<td>48 (4%)</td>
<td>59 (5%)</td>
</tr>
<tr>
<td>Genital ulcers in previous 3 months</td>
<td>242 (21%)</td>
<td>252 (22%)</td>
</tr>
</tbody>
</table>

**Clinical diagnoses by self-report**

- Pneumonia* | 54 (5%) | 50 (4%) | 24 (4%) | 17 (3%) |
- Tuberculosis* | 31 (3%) | 39 (3%) | 22 (4%) | 29 (5%) |
- Herpes zoster* | 37 (3%) | 39 (3%) | 29 (5%) | 25 (5%) |

**Physical examination findings**

- Lymphadenopathy | 148 (13%) | 162 (14%) | 92 (16%) | 94 (18%) |
- Oral candidiasis | 5 (0%) | 2 (0%) | 3 (1%) | 4 (1%) |
- Herpes zoster | 11 (1%) | 13 (1%) | 10 (2%) | 5 (1%) |
- Genital ulcer disease | 38 (3%) | 35 (3%) | 12 (2%) | 12 (2%) |

Data are median (IQR) or n (%). *In previous year.
100%. This adherence measure assesses study-drug coverage during follow-up and accounts for drug not dispensed (mainly for missed visits and pregnancy). Participants contributed to adherence data until the time of the composite endpoint. With a post-randomisation subgroup analysis, we assessed the effect of study-drug coverage over time on the risk of development of the composite primary endpoint. For this analysis, we analysed drug coverage averaged for every 3 months of study follow-up as a time-varying covariate, and categorised coverage as less than 75%, 75–89%, or 90% or higher.

We calculated the number of participants who would need treatment with aciclovir to prevent one event in 1 year (the number needed to treat) for drug not dispensed (mainly for missed visits and pregnancy). Participants contributed to adherence data during follow-up and for accounts for drug not dispensed (mainly for missed visits and pregnancy).

Participants were censored upon reaching primary composite HIV-1 disease progression endpoint. Adherence data were missing for 8.5% of 3-monthly visits. Visit-specific data were calculated as the product of overall dispensed drug taken and proportion of participants to whom drug was dispensed.

<table>
<thead>
<tr>
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<tr>
<td>Study drug coverage</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aciclovir</td>
<td>94.2%</td>
<td>92.4%</td>
<td>90.0%</td>
<td>88.4%</td>
<td>87.9%</td>
<td>88.8%</td>
<td>88.2%</td>
</tr>
<tr>
<td>Placebo</td>
<td>93.6%</td>
<td>91.9%</td>
<td>89.7%</td>
<td>88.2%</td>
<td>88.0%</td>
<td>89.3%</td>
<td>89.7%</td>
</tr>
<tr>
<td>Participants with 90% or higher drug coverage</td>
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<td></td>
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</tr>
<tr>
<td>Aciclovir</td>
<td>84.1%</td>
<td>85.0%</td>
<td>85.3%</td>
<td>84.0%</td>
<td>82.1%</td>
<td>84.7%</td>
<td>82.9%</td>
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<tr>
<td>Placebo</td>
<td>82.8%</td>
<td>84.5%</td>
<td>85.0%</td>
<td>82.2%</td>
<td>80.8%</td>
<td>83.3%</td>
<td>84.3%</td>
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Table 2: Study-drug coverage during follow-up by study group

<table>
<thead>
<tr>
<th>Aciclovir</th>
<th>Placebo</th>
<th>Total events</th>
<th>HR (95% CI)</th>
<th>p value</th>
<th>NNT†</th>
</tr>
</thead>
<tbody>
<tr>
<td>n7</td>
<td>Events</td>
<td>Person-years at risk</td>
<td>Rate (per 100 person-years)</td>
<td>n7</td>
<td>Events</td>
</tr>
<tr>
<td>1686</td>
<td>284</td>
<td>2446</td>
<td>11.6</td>
<td>1677</td>
<td>324</td>
</tr>
</tbody>
</table>

Table 3: Effect of aciclovir on measures of HIV-1 disease progression during study follow-up

NNT=number needed to treat. ART=antiretroviral therapy.*Number of participants who had at least one follow-up visit with endpoint assessed. †Number of people co-infected with HIV-1 and herpes simplex virus type 2 needed to treat with aciclovir 400 mg twice daily for 1 year to prevent one person reaching the HIV-1 disease-progression endpoint. ‡Excluding ART initiated for prevention of mother-to-child transmission (PMTCT). §Censored at first report of ART use (other than short-course PMTCT). ¶Assessed only for those who had CD4 cell counts of 350 cells per μL or higher at baseline; this endpoint was added post hoc after study unblinding.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors designed the study and wrote the protocol, had full access to the raw data, and are solely responsible for the overall study design, data analysis, and writing of the report.
participants had asymptomatic HIV-1 disease, with 5% or fewer reporting pneumonia, tuberculosis, or herpes zoster in the previous year. Retention of participants at 24 months of follow-up was 92% overall (figure 1). Participants contributed 4826 person-years of follow-up for analysis of the primary composite endpoint. A total of 96·3% of dispensed doses were taken and 93·7% of monthly study drug dispensed, resulting in overall drug coverage of 90·2% (table 2). During every 3-month study follow-up, 80·8–85·3% of participants achieved 90% or higher drug coverage.

During follow-up, 9·1 participants per 100 person-years had CD4 cells counts fall to fewer than 200 cells per μL, 6·7 per 100 person-years started antiretroviral therapy, excluding therapy started for PMTCT, and 1·2 per 100 person-years died. Deaths were attributed to pneumonia (n=13), tuberculosis (ten), gastrointestinal infections (seven), other infectious processes (six), malaria (five), and other causes (20). Two participants in the aciclovir group and two in the placebo group died from trauma. Six participants in the aciclovir group and five in the placebo group died after starting antiretroviral therapy; these deaths were not included in the analyses. Of participants given antiretroviral therapy, the median CD4 cell count before this therapy was started was 195 cells per μL (IQR 159–246), with 34% given antiretrovirals with CD4 cell counts between 200 and 350 cells per μL and 11% with counts higher than 350 cells per μL.

Table 3 and figure 2 show the comparison between disease progression outcomes by study group; 16% (40) fewer participants in the aciclovir group than in the placebo group reached the primary composite endpoint. Of the 608 composite endpoints, 425 (70%) had CD4 cell count falling to fewer than 350 cells per μL, 6·7 per 100 person-years started antiretroviral therapy; these deaths were not included in the analyses. Of participants given antiretroviral therapy, the median CD4 cell count before this therapy was started was 195 cells per μL (IQR 159–246), with 34% given antiretrovirals with CD4 cell counts between 200 and 350 cells per μL and 11% with counts higher than 350 cells per μL.

We assessed the effect of aciclovir on the composite measure of HIV-1 disease progression within pre-specified subgroups that were defined by sex, baseline HIV-1 plasma RNA concentration, and baseline CD4 cell count (figure 3). We identified no statistically significant differences. The intervention seemed less effective in those with CD4 cell counts of less than 500 cells per μL, but this difference was not significant (figure 3). Effectiveness of the intervention against HIV-1 was higher in participants with study-

Figure 2: Cumulative probability of select HIV-1 disease progression endpoints (Kaplan-Meier estimates) by treatment group: (A) Composite disease progression endpoints* (B) CD4 cell count fewer than 350 cells per μL†

*Endpoints of 3363 individuals (HR=0·84 95% CI 0·71–0·98, p=0·03). Primary composite endpoint, defined as first occurrence of CD4 cell count falling to fewer than 350 cells per μL, non-pregnant mother-to-child transmission antiretroviral therapy initiation, or non-trauma death. †Endpoint for 2431 individuals. First occurrence of CD4 cell count falling to fewer than 200 cells per μL, non-pregnant mother-to-child transmission antiretroviral therapy initiation, or non-trauma death.

The intervention seemed less effective in those with CD4 cell counts of less than 500 cells per μL, but this difference was not significant (figure 3). Effectiveness of the intervention against HIV-1 was higher in participants with study-

Results

Figure 1 shows the trial profile. Baseline demographic and clinical characteristics were similar between the two study groups (table 1). 68% of participants were women. The median baseline CD4 cell count was 462 cells per μL (IQR 347–631) and for HIV-1 plasma RNA was 4·1 log10 copies per μL (3·4–4·7). Most
drug coverage of more than 90% than it was in those with less than 90% drug coverage, but this difference was not significant.

Overall, 3·3% of expected follow-up time was missing (3·2% in the aciclovir group and 3·5% in the placebo group). In sensitivity analyses, the RR for the composite primary endpoint varied between 0·81 and 0·86. Assuming that the incidence of infection during follow-up periods was identical in both groups and equal to the observed incidence in the placebo group, the sensitivity-adjusted RR was 0·84 (p=0·03). Assuming that the rate of HIV-1 disease progression was not significant.

Outcome of interest varied between 0·81 and 0·86. Fewer participants in the aciclovir group than in the placebo group had CD4 cell counts fall below 200 cells per μL (p=0·06), or died from non-trauma-related reasons (p=0·29). Furthermore, fewer of those in the group assigned aciclovir with CD4 cell counts of fewer than 350 cells per μL by 28·8 months (35·1 months for aciclovir vs 28·8 months for placebo).

Discussion

Our results show that standard doses of aciclovir for suppression of herpes simplex virus type 2 in people infected with HIV-1 and herpes type 2 reduced the risk of HIV-1 disease progression by 16%. Fewer participants in the aciclovir group than in the placebo group had CD4 cell counts fall below 200 cells per μL (p=0·06), started antiretroviral therapy (p=0·05), or died from non-trauma-related reasons (p=0·29). Furthermore, fewer of those in the group assigned aciclovir with CD4 cell counts of fewer than 350 cells per μL by 6·3 months (35·1 months for aciclovir vs 28·8 months for placebo).

Figure 3: Subgroup analyses for effect of aciclovir on primary composite endpoint

Three participants died within first month of study and were excluded from analysis. Data could not be classified for 9% of visits because of missing data for study-drug adherence. *Number of participants with follow-up and endpoints assessed at least once during follow-up. †Study-drug coverage was averaged per quarter of follow-up and analysed as a time-dependent variable; thus, participants could have contributed to more than one category during follow-up, so total numbers of participants are not given (··).
We have previously reported that aciclovir reduced HIV-1 plasma RNA by 0.25–0.5 log₁₀ copies per μL in this trial population. This result was similar to that reported in previous trials of short-term suppression of herpes simplex virus type 2 (1–3 months), showing a 0.25–0.5 log₁₀ reduction in HIV-1 concentrations (figure 4). We infer that the reduction in HIV-1 concentrations during aciclovir suppression mediated a reduction in risk of HIV-1 disease progression. In results of a systematic review of US and African observational studies, a 0.3 log₁₀ copies per μL reduction in plasma HIV-1 concentrations predicted a reduced risk of HIV-1 progression by 25%, lending support to our postulation. Our results show that a strategy without antiretroviral therapy (ie, with herpes type 2 suppression) can modestly delay HIV-1 disease progression.

In early studies of zidovudine monotherapy, similar reductions in HIV-1 plasma RNA and a decreased risk of disease progression and mortality were reported. Zidovudine effects waned during 3–6 months, because resistant HIV-1 variants were selected. Aciclovir is a highly specific chain terminator to the herpes simplex virus, needing thymidine kinase from the herpes virus for initial phosphorylation, and is preferentially incorporated by the herpes virus DNA polymerase. This mechanism, in conjunction with the reported 73% reduction in the frequency of type 2 herpes-positive genital ulcer disease in those randomised to aciclovir in our study, led us to postulate that aciclovir’s effect in reduction of HIV-1 concentrations is mediated through suppression of herpes.

Notably, results of in-vitro studies suggest that aciclovir could directly inhibit HIV-1 replication, possibly through kinases from other ubiquitous herpes viruses (eg, human herpes virus 6). Findings from an in-vivo study with high-dose aciclovir showed selection of an uncommon HIV-1 mutation—V75I. However, the 0.25 log₁₀ average decreased plasma HIV-1 concentrations observed in our study persisted during 24 months of follow-up without an HIV-1 plasma RNA rebound, contrary to what might be expected from selection of resistant variants. In future investigations, we will assess incidence of HIV-1 mutations in the aciclovir versus placebo groups during follow-up to assess specific mechanisms underlying HIV-1 plasma RNA reductions.

Alicloivir has a much lower frequency of adverse effects than do many antiretroviral therapy regimens that are used in resource-poor settings. We identified no serious adverse events associated with aciclovir. This drug was well tolerated, which probably contributed to the high adherence in our study. Additionally, the absence of a need for specific laboratory monitoring for aciclovir toxicity during herpes suppression is especially important when laboratory infrastructure for monitoring and access to care are restricted. Our selection of a standard dose of aciclovir (similar to valaciclovir 500 mg twice daily) was based on efficacy of this dose in reduction of frequency of symptomatic genital ulcer disease and asymptomatic reactivation of type 2 genital herpes in dually infected people, a well-documented safety profile, generic availability, and a relatively low cost. A meta-analysis of several small studies of high-dose (≥3200 mg per day) aciclovir for suppression of herpes virus type 2 in conjunction with mononucleoside or dual nucleoside antiretroviral therapy identified a similar magnitude of effect on HIV-1 associated mortality (HR 0.78, 95% CI 0.65–0.93) to that reported in our study. Whether increased doses of herpes suppressive therapy have a heightened effect on HIV-1 plasma concentrations and disease progression needs to be investigated.

Further investigation is needed to determine cost-effectiveness and clinical and public health effects of suppression of herpes simplex virus 2 to slow HIV-1 disease progression until dually infected people reach guidelines for antiretroviral therapy initiation. Table 4 shows our summary results in the context of other non-antiretroviral therapy biomedical interventions that were investigated for their effect on measures of HIV-1 disease progression. Trimethoprim-sulfamethoxazole prophylaxis and multivitamins in people infected with HIV-1 have become standard practice in many resource-poor settings, on the basis of trials showing a reduction in HIV-1 associated mortality of about 45% with trimethoprim-sulfamethoxazole and 27% with multi-

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**Table 4: Comparison of biomedical clinical trials of non-antiretroviral therapy interventions to reduce HIV-1 disease progression**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Estimate of effect HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Tanzania (pregnant women)</td>
<td>WHO stage 4 or death 0.71 (0.51 to 0.98)</td>
</tr>
<tr>
<td>Cote d’Ivoire (adults)</td>
<td>Death 0.54 (0.35 to 0.84)</td>
</tr>
<tr>
<td>South Africa (adults)</td>
<td>Death or admission 0.57 (0.42 to 0.75)</td>
</tr>
<tr>
<td>Uganda (adults)</td>
<td>Death 0.54 (0.35 to 0.84)</td>
</tr>
<tr>
<td>Co-trimoxazole for prophylaxis of bacterial infections</td>
<td>Change in HIV-1 plasma RNA 0.54 (1.17 to 0.99)</td>
</tr>
<tr>
<td>Kenya (adults)</td>
<td>HIV-1 plasma RNA 0.71 (0.51 to 0.98)</td>
</tr>
<tr>
<td>Co-trimoxazole for prophylaxis and multivitamins in people infected with HIV-1</td>
<td>WHO stage 4 or death 0.71 (0.51 to 0.98)</td>
</tr>
<tr>
<td>Albendazole for treatment of helmint infection</td>
<td>Death 0.54 (0.35 to 0.84)</td>
</tr>
<tr>
<td>HIV-2 suppression (aciclovir)</td>
<td>Change in HIV-1 plasma RNA 0.71 (0.51 to 0.98)</td>
</tr>
<tr>
<td>Alma na of 8 randomised</td>
<td>Death 0.54 (0.35 to 0.84)</td>
</tr>
<tr>
<td>High dose oral (&gt;3200 mg per day)</td>
<td>Death 0.28 (0.21 to 0.37)</td>
</tr>
<tr>
<td>Adults from east and southern African (present study)</td>
<td>First of CD4 cell count fewer than 200 cells per μL, ART initiation, or death 0.84 (0.71 to 0.98)</td>
</tr>
</tbody>
</table>

Table 4: Comparison of biomedical clinical trials of non-antiretroviral therapy interventions to reduce HIV-1 disease progression
vitamins. However, such non-antiretroviral therapy interventions to reduce HIV-1 disease progression were undertaken in the era before combination antiretroviral therapy was widely available, and thus included follow-up of people with advanced disease. Furthermore, in subgroup analyses,16 trimethoprim-sulfamethoxazole had greatest efficacy in individuals with CD4 cell counts fewer than 200 cells per μL or symptoms of advanced immunosuppression. By contrast, we identified that suppression of type 2 herpes virus delayed HIV-1 disease progression in a low-resource setting in men and women with a wide range of ages and CD4 cell counts of 250 cells per μL or higher at enrolment.

The International AIDS Society-USA Panel17 revised recommendations to start antiretroviral therapy at CD4 cell counts of fewer than 350 cells per μL in some settings. Early initiation of antiretroviral therapy on will probably have a greater effect on disease progression than we noted with aciclovir in this study, and might have an ancillary benefit of reduction of HIV-1 transmission. However, availability of resources are insufficient in many settings to provide this therapy even to those with CD4 counts of fewer than 200 cells per μL.6 Furthermore, in view of the interest in identification of interventions for people with high counts, we need further detailed investigation of suppression of herpes simplex virus type 2 in people with counts of more than 500 cells per μL. Results of a cost-effectiveness analysis25,26 showed that herpes virus type 2 suppression meets the World Development Report cost-effectiveness threshold ($1000 per life-year gained) at the lowest available pricing for generic aciclovir ($25 per year for twice daily aciclovir 400 mg tablets). However, the local pricing of aciclovir varies widely, and can exceed the international reference price by 6–10-fold in sub-Saharan Africa.27 Efforts are needed to improve drug procurement, distribution, and access throughout sub-Saharan Africa for aciclovir to have a maximum effect on the HIV-1 epidemic. Mathematical modelling could be useful to define how to best use herpes simplex virus 2 suppression to affect the HIV-1 epidemic. Such modelling could be used to quantify the benefits, costs, and potential effect of implementation of such suppression or other non-antiretroviral therapy strategies compared with previous antiretroviral therapy initiation to delay HIV-1 disease progression.

One limitation of our study was the low frequency of diagnostic testing and autopsies to inform the causes of death. Furthermore, although most participants were given antiretrovirals at CD4 counts of 200 cells per μL or fewer, reasons for therapy initiation at counts higher than 200 cells per μL were not recorded because antiretroviral care was generally provided outside the study clinics. Trimethoprim-sulfamethoxazole prophylaxis data were also not gathered at all sites; however, at five sites where this information was recorded, participants reported trimethoprim-sulfamethoxazole use at 73% of follow-up visits, and this use did not differ by treatment group (data not shown). Finally, although findings of studies suggest HIV-1 disease progression might differ by HIV-1 subtype,28 subtype data are not available for our cohort and will be assessed in future analyses.

We have shown that aciclovir for herpes simplex virus type 2 suppression in people dually infected with HIV-1 and herpes type 2 with CD4 cell counts higher than 250 cells per μL who are not taking antiretroviral therapy can modestly reduce risk of HIV-1 disease progression. Further investigation is needed to establish if suppression of this herpes virus has a role in HIV-1 treatment for people not eligible for antiretroviral therapy.

Contributors
The core protocol team (CC, AW, JRL, JMB, LC, AM, and JPH) designed the study, and JPH and KT undertook the primary data analysis. All investigators contributed to gathering of data, reviewed report drafts, and approved the final manuscript. JRL, JMB, and CC wrote the first draft.

Conflicts of interest
CC has received research grant support from GlaxoSmithKline (GSK), which did not include salary support, and has served on an advisory board for this company; AW has received grant support from Astellas, GSK, and Antigenics, and has been a consultant for Astellas and Aicuris; KF has received research grant funding from Astellas Pharma USA and GSK; LC is a consultant for Aicuris and GenPhar and is the head of the Scientific Advisory Board of Immune Design, receiving financial remuneration for this position, including equity shares that are less than 1% ownership. University of Washington Virology Division Laboratories have received grant funding from GSK and Novartis to undertake herpes simplex virus serological assays and PCR assays for studies funded by these companies; LC directs these laboratories, but receives no salary support from these grants.

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