Acyclovir Prophylaxis Reduces the Incidence of Herpes Zoster Among HIV-Infected Individuals: Results of a Randomized Clinical Trial

Ruane V. Barnabas,1,2,3 Jared M. Baeten,2,3 Jairam R. Lingappa,1,2 Katherine K. Thomas,1 James P. Hughes,4,4 Nelly R. Mugo,1 Sinead Delany-Moretuve,5 Glenda Gray,7 Helen Rees,7 Andrew Mujugira,1,3 Allison Ronald,10 Wendy Stevens,8 Saidi Kapiga,11 Anna Wald,1,2,5,6 and Connie Celum1,2,3; for the Partners in Prevention HSV/HIV Transmission Study Team

Departments of 1Global Health, 2Medicine, 3Epidemiology, 4Biostatistics, 5Laboratory Medicine, 6Cancer Research Center, Seattle, Washington; 7Wits Reproductive Health and HIV Institute, and 8Department of Molecular Medicine and Haematology, University of the Witwatersrand, Johannesburg, 9Perinatal HIV Research Unit, Soweto, South Africa; 10Department of Medicine, University of Manitoba, Winnipeg, Canada; and 11Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, United Kingdom

Human immunodeficiency virus (HIV)–infected persons have higher rates of herpes zoster than HIV-uninfected individuals. We assessed whether twice daily treatment with 400 mg of oral acyclovir reduces the incidence of herpes zoster in an HIV-infected study performed in a randomized, double-blind, placebo-controlled trial among 3408 persons coinfected with HIV and herpes simplex virus type 2. During 5175 person-years of follow-up, 26 cases of herpes zoster occurred among those assigned acyclovir, compared with 69 cases among those assigned placebo (rates, 1.00 and 2.68/100 person-years, respectively), a relative decrease of 62% (hazard ratio, 0.38; 95% confidence interval, 0.24–0.67; P < .001). Daily acyclovir prophylaxis significantly reduced herpes zoster incidence among HIV-infected persons.

Keywords. herpes zoster; acyclovir; HIV; acyclovir prophylaxis; shingles; VZV.

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Acyclovir prophylaxis reduces the incidence of herpes zoster in a randomized, double-blind, placebo-controlled trial of acyclovir (400 mg twice daily), among 3408 HIV-infected women and men from 7 African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia) who were coinfected with herpes simplex virus type 2 (HSV-2). The primary aim of the study was to assess the impact of acyclovir prophylaxis on HIV transmission to HIV-uninfected heterosexual partners; as previously reported, no reduction in HIV transmission was seen, although acyclovir prophylaxis did reduce the frequency of genital ulcers due to HSV-2 and resulted in a modest reduction in plasma HIV RNA load (0.25 log10 copies/mL) [8]. A predefined secondary outcome of the trial was incident herpes zoster. VZV serologic assays were not performed. Eligible participants reported no current use of ART, and all had CD4+ T-cell counts of ≥250 cells/µL and no history of AIDS-defining conditions. The University of Washington Human Subjects Review Committee and ethics review committees at the each of the collaborating organizations approved the study protocol. All participants provided written informed consent.

Methods

Study Design and Participants

Between November 2004 and April 2007, we conducted the Partners in Prevention HSV/HIV Transmission Study [8], a randomized, double-blind, placebo-controlled trial of acyclovir (400 mg twice daily), among 3408 HIV-infected women and men from 7 African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia) who were coinfected with herpes simplex virus type 2 (HSV-2). The primary aim of the study was to assess the impact of acyclovir prophylaxis on HIV transmission to HIV-uninfected heterosexual partners; as previously reported, no reduction in HIV transmission was seen, although acyclovir prophylaxis did reduce the frequency of genital ulcers due to HSV-2 and resulted in a modest reduction in plasma HIV RNA load (0.25 log10 copies/mL) [8]. A predefined secondary outcome of the trial was incident herpes zoster. VZV serologic assays were not performed. Eligible participants reported no current use of ART, and all had CD4+ T-cell counts of ≥250 cells/µL and no history of AIDS-defining conditions. The University of Washington Human Subjects Review Committee and ethics review committees at the each of the collaborating organizations approved the study protocol. All participants provided written informed consent.

Procedures

Throughout the study, all participants received individualized, confidential HIV counseling, risk-reduction counseling,
couples counseling, free condoms, and treatment of sexually transmitted infections according to World Health Organization guidelines. HIV-infected participants were seen once per month for provision of study medication (acyclovir 400 mg twice daily or matching placebo). CD4+ T-cell counts were assessed every 6 months, and the plasma HIV RNA load was measured at baseline. Herpes zoster detected at a monthly visit was documented during physical examination; once each quarter, a medical history was obtained to record self-reported zoster not observed at a regular visit. During the quarterly medical visits, clinicians asked participants whether they had had any skin rash consistent with zoster and recorded reported cases.

At the quarterly visits, participants were asked whether they had received ART since the last visit, and whether those who initiated ART continued to receive treatment during follow-up. At the time the study was undertaken, national guidelines generally recommended ART initiation for patients with CD4+ T-cell counts of ≤200–250 cells/µL or clinical AIDS. Participants who met national guidelines for initiation of ART during follow-up, as a result of a decline in CD4+ T-cell count or a change in clinical status, were referred to local HIV clinics for ART. HIV-infected women who became pregnant during the study were referred to antenatal clinics for services to prevent mother-to-child transmission.

Statistical Analysis
For the present analysis, the primary outcome was an episode of herpes zoster during follow-up, either observed on examination or reported by the participant. The primary analysis was intention to treat, and survival analysis was used to estimate the effect of acyclovir prophylaxis on herpes zoster incidence in the acyclovir arm, compared with the placebo arm. Multiple visits with an event within the same quarter were rare and were treated as one episode; events in different quarters were treated as separate events. Cox regression with the Anderson–Gill counting method and robust variance was used to include multiple events per participant in the survival analysis. A second survival analysis, using only time to the first zoster event, was used to create cumulative probability curves for zoster incidence and to compare curves by arm, using the log-rank test. To explore the impact of ART on zoster incidence, and because HIV-infected persons receiving ART continue to have an increased risk of zoster as compared to uninfected individuals [6] and because ART initiation is associated with a short-term increase in the risk of herpes zoster [6], data were not censored at ART initiation. Data were analyzed using SAS (version 9.3; Cary, North Carolina).

RESULTS
The Partners in Prevention HSV/HIV Transmission Study enrolled 3381 participant infected with HIV and HSV–2, with 1693 were randomized to acyclovir and 1688 to placebo. As detailed elsewhere [8], two thirds of participants were women, the median age was 32 years, the median CD4+ T-cell count was 462 cells/µL, and randomization was balanced with respect to these characteristics. Four percent in each arm reported a history of herpes zoster in the prior year, and 1% in each arm had zoster on baseline clinical examination.

During 24 months, the study accrued 2605 person-years of follow-up in the acyclovir arm and 2570 person-years of follow-up in the placebo arm. The median follow-up time was 20 months. Acyclovir adherence, assessed by pill count and self-report, was high, with an estimated 96% of doses dispensed consumed and drug consumed on 90% of days overall. A total of 151 participants in the acyclovir arm initiated ART, compared with 180 participants in the placebo arm [9], resulting in 125 and 158 person-years at risk while receiving ART in the acyclovir and placebo groups, respectively.

Ninety-five cases of herpes zoster occurred during follow-up, of which 15 were observed by skin examination only, 62 were self-reported as occurring between study visits, and 18 were documented by both examination and self-report. Of these 95 herpes zoster events, 26 occurred in 22 people in the acyclovir arm (incidence, 1.00 cases/100 person-years), compared with 69 in 64 people in the placebo arm (incidence, 2.68 cases/100 person-years; Table 1). The cumulative proportion of participants with herpes zoster during the study was 4.5% (95% CI, 3.5%–5.8%) in the placebo arm and 1.7% (1.1%–2.5%) in the acyclovir arm (P < .001 for the difference in time to first event; Figure 1). Overall, analysis of all events revealed that acyclovir prophylaxis decreased the incidence of herpes zoster by 62% in the acyclovir arm, compared with the placebo arm (hazard ratio [HR], 0.38; 95% CI, .24–.67; P < .001). The protective effect of acyclovir on zoster was not modified by sex, age (<30 years and ≥30 years), CD4+ T-cell count (≤350 and >350 cells/µL; ≤250 and >250 cells/µL), or baseline plasma HIV RNA load (<10 000, 10 000–99 999, and ≥100 000 copies/mL).

There were 6 cases of herpes zoster among 6 participants who initiated ART after study enrollment; all were in the placebo arm, and all occurred during the first 3 months after ART initiation (range, 3–77 days). Incidence in the placebo arm was 3.80 cases/100 person-years, compared with 0.00 cases/100 person years in the acyclovir arm (HR, 0.00; 95% CI, .00–1.08). ART did not significantly modify the effect of acyclovir on zoster (P = .41), but the number of participants receiving ART was small. Acyclovir did not prevent zoster recurrences among persons reporting prior zoster episodes at baseline (HR, 1.82; 95% CI, .33–9.96) but did prevent recurrences among participants who had not experienced zoster prior to enrollment (HR, 0.29; 95% CI, .18–.49; P for interaction = .01).

DISCUSSION
In this randomized, double-blind, placebo-controlled trial of acyclovir 400 mg twice daily among African HIV-infected persons, acyclovir prophylaxis substantially reduced herpes zoster events by 62% regardless of sex, age, CD4+ T-cell count, plasma
HIV RNA load, or ART use. This reduction in herpes zoster events was consistent with a study from 1999 that found a 68% reduction in herpes zoster with high-dose acyclovir [7].

The incidence of herpes zoster (2.68 cases/100 person-years in the placebo arm) in this population was comparable to previous estimates among HIV-infected individuals (2.90 cases/100 person-years), which is 12–17-fold higher than their age-matched HIV-uninfected controls [5].

Among immunocompromised individuals, including HIV-infected persons, herpes zoster may have a prolonged course and disease recurrence is more common [4]. Acyclovir prophylaxis did not prevent zoster recurrence among persons who reported prior episodes in our study, which might indicate a defect in VZV-specific T-cell immunity [10]; HIV-infected individuals with prior zoster may require a higher acyclovir dose for prophylaxis.

The limitations of our study were the small numbers of participants with low CD4+ T-cell counts, because such persons were excluded from enrollment. Previous studies have found an increased incidence of herpes zoster with declining CD4+ T-cell count [11, 12], which we did not observe, perhaps because of limited power. Some studies have shown an increase in the risk of herpes zoster immediately after ART initiation [6], which is thought to be due to immune reconstitution inflammatory syndrome. We did not observe ART to alter the incidence of herpes zoster events, although the number of individuals and duration of ART in our study were small.

Current Advisory Committee on Immunization Practices guidelines recommend zoster immunization for immunocompetent persons beginning at age 60 years. Because of the risk of vaccine-associated zoster, the zoster vaccine is contraindicated in immunocompromised persons, including HIV-infected

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### Table 1. Herpes Zoster Incidence, by Treatment Arm

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acyclovir Arm</th>
<th>Placebo Arm</th>
</tr>
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<tbody>
<tr>
<td>Subjects, No. Events, No. PY at Risk, Rate, Cases/100 PY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall efficacy</td>
<td>1693 26 2605 1.00</td>
<td>1686 69 2570 2.68</td>
</tr>
<tr>
<td>Zoster observed on examination</td>
<td>1693 12 2604 0.46</td>
<td>1688 21 2570 0.82</td>
</tr>
<tr>
<td>Report of zoster</td>
<td>1693 16 2603 0.61</td>
<td>1688 64 2568 2.49</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Subgroup, based on enrollment characteristics</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>561 10 875 1.14</td>
<td>536 28 838 3.34</td>
</tr>
<tr>
<td>Female</td>
<td>1132 16 1730 0.93</td>
<td>1152 41 1732 2.37</td>
</tr>
</tbody>
</table>

Effect modification:

| Age, y                                        |                      |             |
|<30                                           | 664 13 1011 1.29      | 665 24 991 2.42 |
|≥30                                           | 1028 13 1593 0.82     | 1023 45 1579 2.85 |

Effect modification:

| CD4 T-cell count, cells/µL                    |                      |             |
|<350                                          | 424 8 648 1.23        | 461 34 703 4.84 |
|≥350                                          | 1269 18 1967 0.92     | 1227 35 1867 1.87 |

Effect modification:

| Viral load, copies/mL                         |                      |             |
|<10,000                                       | 778 6 1190 0.50       | 800 17 1214 1.40 |
|10,000–99,999                                 | 645 12 1004 1.20      | 641 28 986 2.84 |
|≥100,000                                      | 253 8 325 2.08        | 232 24 348 6.90 |

Effect modification:

| ART use in period before clinical visit       |                      |             |
|Yes                                           | ... 0 125 0.00        | ... 6 158 3.80 |
|No                                            | ... 26 2480 1.05      | ... 63 2412 2.61 |

Effect modification:

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; PY, person-years.

a Unless otherwise indicated, data were determined using Cox regression with the Anderson–Gill counting method, to allow multiple outcomes per participant.

b Data denote the incidence rate ratio and exact 95% CI.

c Evaluated using the likelihood ratio test.

d Evaluated using exact logistic regression, to model discrete survival time.
persons with CD4+ T-cell count of <200 cells/µL [4, 13]. Immununospressed persons, including transplant recipients, who receive antiviral prophylaxis against cytomegalovirus (CMV) or HSV with valganciclovir, ganciclovir, valacyclovir, or acyclovir have a lower risk of herpes zoster [14]. Our data contribute to this evidence by demonstrating prevention of herpes zoster in the setting of acyclovir suppressive therapy for HSV-2.

In summary, in this large placebo-controlled trial of daily acyclovir (400 mg twice daily) for HSV-2 suppression, we found a 68% reduction in zoster events on the acyclovir arm. Acyclovir is well tolerated, safe, and affordable as a generic product, and acyclovir prophylaxis has benefits that include a 73% reduction in HSV-2 genital ulcer disease [8] and a modest (16%) decrease in HIV disease progression [9]. For immununospressed patients on antiviral prophylaxis for CMV or HSV, prevention of herpes zoster is an additional benefit. Future research should include a focus on the impact of acyclovir (or related antiviral) prophylaxis on herpes zoster incidence among HIV-infected persons with a low CD4+ T-cell count and among HIV-infected individuals initiating ART, which are the factors associated with greatest frequency of zoster reactivation.

Notes

Acknowledgments. R. V. B. oversaw the analysis and wrote the first draft of the paper, which was revised by all authors. All authors contributed to data analysis, as well as to the interpretation of findings. K. K. T. did the statistical analysis, with input from R. V. B., J. M. B., J. P. H., J. R. L., and C. C. All authors approved the final version of the paper for submission.

The University of Washington human subjects review committee and ethics review committees at the each of the collaborating organizations approved the study protocol. All participants provided written informed consent.

Disclaimer. The work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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