Discontinuation of Secondary Prophylaxis for *Pneumocystis carinii* Pneumonia in Human Immunodeficiency Virus–Infected Patients: A Randomized Trial by the CIOP Study Group

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This subgroup analysis assessing secondary prophylaxis for *Pneumocystis carinii* pneumonia (PCP) describes a multicenter, open-labeled, randomized, controlled trial evaluating the discontinuation of PCP prophylaxis. The main inclusion criterion was a history of PCP and an increase in the CD4 cell count to >200 cells/μL associated with receipt of highly active antiretroviral therapy for ≥3 months. The primary end point was the development of definitive or presumptive PCP. A total of 146 patients were enrolled (77 in the treatment discontinuation arm). After >2 years, 1 definitive and 1 presumptive case of PCP were observed, both of which occurred in patients who discontinued therapy. In most patients, secondary prophylaxis for PCP can be safely discontinued after potent antiretroviral therapy is initiated, but the threshold of >200 CD4 cells/μL may not be considered absolutely safe. Patients who present with symptoms after discontinuation of secondary prophylaxis should be evaluated for PCP despite high CD4 count and complete virus suppression.

The use of HAART for HIV infection has resulted in improved survival and in an increase in the time that individuals remain free of opportunistic infections [1, 2], presumably as a result of the improvement of the immune system. Even in persons with extremely severe immunodeficiency, the CD4 cell count often increases to more than the level considered at risk for the development of opportunistic infections.

Many observational studies and randomized controlled trials [3–18] have been conducted to evaluate whether this CD4 cell recovery can protect against several opportunistic infections. Three previous studies (1 randomized study and 2 observational studies) demonstrated that discontinuing secondary prophylaxis for *Pneumocystis carinii* pneumonia (PCP) in persons treated with HAART was safe [9, 10, 12]. The main limitations of these studies were (1) that they could not...
detect a CD4 cell count threshold greater than which it is safe to discontinue prophylactic regimens, and (2) they had short periods of observation. The aim of this randomized study is to evaluate the long-term safety of discontinuation of secondary prophylaxis for PCP.

PATIENTS AND METHODS

The Changes in Opportunistic Prophylaxis (CIOP) Study was designed as an open-label, randomized, controlled trial. Persons undergoing primary prophylaxis for PCP and toxoplasmic encephalitis began to be enrolled in the study in January 1998 [8]; persons receiving secondary prophylaxis for PCP began to be enrolled in June 1998. Trial participants were enrolled at 41 clinical centers located throughout Italy. Determination of CD4 count and plasma virus level was performed at each site. Lymphocyte subpopulations were measured at all centers by 3-color flow cytometry. HIV RNA levels were determined with use of either a PCR assay (Amplicor HIV-1 Monitor Assay; Roche Molecular Systems) or a branched-chain DNA assay (Chiron). Until the end of 1999, all clinical centers used techniques with a lower limit of detection of 400 copies/mL and 500 copies/mL for PCR and branched-chain DNA assay, respectively; after that date, all clinical centers used ultrasensitive tests with respective lower limits of detection of 20 copies/mL and 50 copies/mL. All data analyses were performed at the trial’s coordinating center (Clinic of Infectious and Tropical Diseases, University of Modena and Reggio Emilia, Modena, Italy).

Inclusion and exclusion criteria. To be included in the study, individuals were required to be HIV seropositive, to be >18 years old, to have a CD4 count of <200 cells/μL at time of initiation of HAART, to have recovered from a confirmed or presumptive episode of PCP, and to be undergoing one of the following regimens of secondary prophylaxis against PCP: trimethoprim-sulfamethoxazole, aerosolized pentamidine, atovaquone, dapsone alone, or dapsone plus pyrimethamine. Participants also had to be receiving HAART, defined as a combination of ≥3 antiretroviral agents, including nucleoside reverse-transcriptase inhibitors plus protease inhibitor and/or one nonnucleoside reverse-transcriptase inhibitor. Furthermore, the CD4 count cell had to have increased to >200 cells/μL on 2 consecutive measurements obtained ≥1 month apart in the 3 months before enrollment. Virus load was not an eligibility criterion. Patients who did not fulfill inclusion criteria were excluded from the study, as were those with a previous episode of toxoplasmic encephalitis. The study was approved by each local ethics committee. All eligible persons had to read and sign an informed consent form.

Randomization. Upon enrollment onto the study, the clinical centers recorded demographic data, dates of previous episodes of PCP, history of prophylaxis against PCP, and history of antiretroviral therapy. This information was sent to the coordinating center, which confirmed that participants fulfilled the inclusion criteria. Within 24 h of receiving this information, the coordinating center randomized participants to 1 of the following 2 study arms: patients who would discontinue secondary prophylaxis against PCP (hereafter referred to as “the discontinuation arm”) and those who would continue prophylaxis (hereafter referred to as “the continuation arm”). The ratio of participants between the 2 arms was 1:1. To reduce potential unbalance among clinical centers, there was a block size every 8 enrolled patients per center [19]. Physical examinations, routine blood control, and CD4 cell count measurements were performed every 2 months; plasma HIV load was measured at least every 4 months. Those participants randomized to the discontinuation arm whose CD4 cell count decreased to ≤200 cells/μL (measured twice, 1 month apart) during the study period were offered to reinitiate prophylaxis and continued to be observed for the entire duration of the study.

End points. The primary end points of the study were a confirmed or a presumptive diagnosis of PCP or death related to this opportunistic infection. The criteria used for a confirmed diagnosis of PCP were the detection of P. carinii cysts (by immunofluorescence) in induced sputum samples and/or bronchoalveolar lavage fluid specimens, or histologic demonstration of microorganisms in transbronchial or open-lung samples obtained by biopsy. The diagnosis of extrapulmonary pneumocystosis was based on the identification of P. carinii in histological or cytological material obtained from extrapulmonary sites.

Presumptive diagnosis was based on the presence of exertional dyspnea and nonproductive cough, bilateral diffuse infiltrates noted on a chest radiograph, abnormal arterial blood gas levels, and unequivocal response to anti-P. carinii therapy in the absence of another diagnosis. The secondary end points consisted of death not related to the primary end points, other HIV infection–related events (i.e., stage B and C events from the Centers for Disease Control and Prevention HIV classification), a CD4 count of ≤200 cells/μL, and events not related to HIV infection. Data regarding side effects and changes in prophylactic regimens and antiretroviral therapy were recorded every 2 months.

Every 6 months, the coordinating center sent clinical monitors to the participating clinical centers to ensure that participants were being selected properly and that accurate data were being provided. The clinical centers were required to report suspected diagnoses of a primary end point to the coordinating center ≤24 h after occurrence.

Statistical analysis. On the basis of pre-HAART data, we assumed that PCP would develop in 15% of patients receiving secondary prophylaxis during the first year of follow-up and in 60% of those who discontinued prophylaxis [20]. We esti-
Table 1. Characteristics of 146 HIV-infected patients who either discontinued or continued receiving prophylaxis for *Pneumocystis carinii* pneumonia, by randomization arm.

<table>
<thead>
<tr>
<th>Characteristic or variable</th>
<th>Patients who discontinued prophylaxis</th>
<th>Patients who continued prophylaxis</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>77 (52.7)</td>
<td>69 (47.3)</td>
<td>.82</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56 (72.7)</td>
<td>49 (71.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21 (27.3)</td>
<td>20 (29.0)</td>
<td></td>
</tr>
<tr>
<td>HIV exposure category</td>
<td></td>
<td></td>
<td>.17</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>38 (49.4)</td>
<td>22 (31.9)</td>
<td></td>
</tr>
<tr>
<td>Male-male sex</td>
<td>14 (18.2)</td>
<td>14 (20.3)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual sex</td>
<td>19 (24.7)</td>
<td>26 (37.7)</td>
<td></td>
</tr>
<tr>
<td>Other or unknown</td>
<td>6 (7.8)</td>
<td>7 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>36.4 (26.9–60.5)</td>
<td>37.3 (26.4–68.3)</td>
<td>.32</td>
</tr>
<tr>
<td>Antiretroviral therapy naive at initiation of HAART</td>
<td>31 (21.2)</td>
<td>31 (21.2)</td>
<td>.57</td>
</tr>
<tr>
<td>Combination antiretroviral therapy received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 NRTIs and indinavir</td>
<td>40 (51.9)</td>
<td>37 (53.6)</td>
<td></td>
</tr>
<tr>
<td>2 NRTIs and ritonavir</td>
<td>10 (13.0)</td>
<td>3 (4.3)</td>
<td></td>
</tr>
<tr>
<td>2 NRTIs and HG-SQV</td>
<td>6 (7.8)</td>
<td>7 (10.1)</td>
<td></td>
</tr>
<tr>
<td>2 NRTIs and nelfinavir</td>
<td>9 (11.7)</td>
<td>10 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 (15.6)</td>
<td>12 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Laboratory value at initiation of combination antiretroviral therapy, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cells, %</td>
<td>3.9 (1.8–7.0)</td>
<td>3.6 (2.0–6.9)</td>
<td>.92</td>
</tr>
<tr>
<td>CD4 cell count, cells/μL</td>
<td>30 (11–84)</td>
<td>33 (14–73)</td>
<td>.55</td>
</tr>
<tr>
<td>HIV RNA, log10 copies/mL</td>
<td>5.20 (4.45–5.69)</td>
<td>5.16 (4.76–5.45)</td>
<td>.74</td>
</tr>
<tr>
<td>Laboratory value at study entry, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cells, %</td>
<td>17 (13.0–22.5)</td>
<td>15.0 (12.6–21.0)</td>
<td>.15</td>
</tr>
<tr>
<td>CD4 count, cells/μL</td>
<td>398 (306–489)</td>
<td>319 (275–423)</td>
<td>.03</td>
</tr>
<tr>
<td>HIV RNA level, log10 copies/mL</td>
<td>1.9 (1.3–4.38)</td>
<td>1.6 (1.40–5.56)</td>
<td>.36</td>
</tr>
<tr>
<td>HIV RNA level of &lt;2.7 log10 copies/mL at study entry</td>
<td>52</td>
<td>44</td>
<td>.76</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. HG-SQV, hard-gel saquinavir; IQR, interquartile range; NRTI, nucleoside reverse-transcriptase inhibitor.

estimated that \( \geq 30 \) patients at risk would be needed in each treatment group to permit us to detect a 45% difference with 90% certainty and a 5% significance level. An analysis was performed that used the intent-to-treat principle. To compare demographic, clinical, virologic, and immunologic characteristics between the 2 treatment arms at enrollment, we used the \( \chi^2 \) test or the Wilcoxon rank-sum test, depending on whether the variable was categorical or continuous. The length of follow-up was calculated as the time that elapsed between the date of randomization and the date of either diagnosis of PCP, death, the first measurement of a CD4 cell count of \( \leq 200 \) cells/μL, or the end of the study, depending on which occurred first. We calculated exact 95% CIs and \( P \) values to compare the 2 groups for the incidence of the end points, having assumed that the events followed a Poisson distribution.

**RESULTS**

Characteristics of the study participants at enrollment. From June 1998 through December 1999, 146 persons were enrolled in the study; 77 were randomized to the discontinuation arm, and 69 were randomized to the continuation arm. Epidemiological characteristics of and immunological and virological values for patients in the 2 groups at the time of initiation of HAART and at the time of study entry are shown in table 1. The secondary prophylactic regimens, the diagnosis of the first episode of PCP, and the median time from PCP diagnosis to the first measurement of a CD4 cell count of \( > 200 \) cells/μL are shown in table 2.

The median durations of secondary prophylaxis before enrollment were 26.6 months in the discontinuation arm and
Table 2. Characteristics of HIV-infected patients who either discontinued or continued receiving prophylaxis for *Pneumocystis carinii* pneumonia (PCP), by secondary prophylactic regimen.

<table>
<thead>
<tr>
<th>Characteristic or variable</th>
<th>Patients who discontinued prophylaxis</th>
<th>Patients who continued prophylaxis</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>77 (52.7)</td>
<td>69 (47.3)</td>
<td>—</td>
</tr>
<tr>
<td>Diagnosis of first episode of PCP</td>
<td></td>
<td></td>
<td>.22</td>
</tr>
<tr>
<td>Presumptive</td>
<td>28 (36.4)</td>
<td>32 (46.4)</td>
<td></td>
</tr>
<tr>
<td>Confirmed</td>
<td>49 (63.6)</td>
<td>37 (53.6)</td>
<td></td>
</tr>
<tr>
<td>Secondary prophylactic regimen received</td>
<td></td>
<td></td>
<td>.82</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>55 (71.4)</td>
<td>48 (69.5)</td>
<td></td>
</tr>
<tr>
<td>Aerosolized pentamidine</td>
<td>17 (22.1)</td>
<td>14 (20.4)</td>
<td></td>
</tr>
<tr>
<td>Dapsone-pyrimethamine</td>
<td>2 (2.6)</td>
<td>4 (5.8)</td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>3 (3.9)</td>
<td>2 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>—</td>
<td>1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Time from diagnosis of PCP to measurement</td>
<td>19.2 (8.3–29.0)</td>
<td>17.4 (9.0–23.5)</td>
<td>.4</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range.

28.0 months in the continuation arm. The median time between initiation of HAART and enrollment in the study was 23.2 months (interquartile range [IQR], 15.8–28.7 months) in the discontinuation arm and 24.6 months (IQR, 18.6–28.4 months) in the continuation arm. The median time from the first available CD4 count of \( <200 \text{ cells}/\mu\text{L} \) to the first CD4 count of \( >200 \text{ cells}/\mu\text{L} \) was 20.6 months (IQR, 8.5–42.8 months) for the discontinuation arm and 16.2 months (IQR, 6.6–24.2 months) for the continuation arm. The median time between the first CD4 cell count of \( >200 \text{ cells}/\mu\text{L} \) and enrollment was 9.9 months (IQR, 5.9–16.6 months) for the continuation arm and 12.8 months (IQR, 6.1–18.8 months) for the discontinuation arm.

**Incidence of primary end points.** The median duration of follow-up was 27.4 months (range, 24.8–29.2 months; 166.7 person-years) for participants randomized to the discontinuation arm and 25.1 months (range, 20.3–28.1 months; 138.6 person-years) for participants in the continuation arm. Two cases of PCP (1 definitive case and 1 presumptive case) were diagnosed among the 146 participants during the study period; both cases occurred in the discontinuation arm.

**Patient 1.** Patient 1 had a definitive diagnosis of PCP. The patient was a 40-year-old man who initiated secondary prophylaxis for PCP in April 1996 with daily doses of trimethoprim-sulfamethoxazole. In October 1997, he began receiving HAART that included indinavir plus 2 nucleoside reverse-transcriptase inhibitors, and, in November 1998, his CD4 cell count increased to \( >200 \text{ cells}/\mu\text{L} \) (341 cells/\mu{L}). In February 2000, when he had a CD4 cell count of 407 cells/\mu{L} and a virus load of \( <20 \text{ copies}/\text{mL} \), he was randomized to the discontinuation arm. In April 2000, when he had a CD4 cell count of 339 cells/\mu{L} (14%) and a plasma HIV load of \( <20 \text{ copies}/\text{mL} \), the patient presented with high fever, cough, and shortness of breath. Chest radiography revealed bilateral interstitial and reticulomicronodular infiltrates. Indirect immunofluorescence examination of induced sputum samples revealed *P. carinii* cysts. The patient was treated with trimethoprim-sulfamethoxazole for 3 weeks, with resolution of the clinical and radiological findings.

**Patient 2.** Patient 2 had a presumptive diagnosis of PCP. The patient was a 38-year-old man who initiated secondary prophylaxis for PCP in April 1997 with daily doses of trimethoprim-sulfamethoxazole and HAART (zidovudine, lamivudine, and indinavir). In June 1999, after 18 months in which he continually had a CD4 cell count of \( <200 \text{ cells}/\mu\text{L} \), the patient was randomized to the discontinuation arm of the study; at this time, his CD4 count was 300 cells/\mu{L} and his virus load was \( <400 \text{ copies}/\text{mL} \). In February 2000, he was treated with intravenously administered corticosteroids for asthma; 1 month later, when he had a CD4 cell count of 357 cells/\mu{L} (16%) and a plasma HIV load of \( <400 \text{ copies}/\text{mL} \), he presented with high fever, cough, and shortness of breath. The arterial PO\(_2\) level was 59 mm Hg, and the lactic acid dehydrogenase level was 697 UI/L. Chest radiography revealed bilateral interstitial and reticulomicronodular infiltrates. Neither examination of an induced sputum sample nor culture of a bronchoalveolar lavage sample revealed *P. carinii* or other pulmonary pathogens. Invasive procedures (i.e., transbronchial biopsy and open-lung biopsy) were not performed. On the basis of clinical evolution and radiological presentation, the patient was treated with tri-
methoprim-sulfamethoxazole for 3 weeks, and the clinical and radiological findings resolved. The prompt response to the anti-PCP therapy led us to exclude the possibility of a nonspecific interstitial pneumonitis.

**Statistical analysis.** The upper Poisson 95% CIs for incidence were 3.3 per 100 person-years for PCP for the discontinuation arm and 2.7 for the continuation arm if 1 event was considered ($P = .55$); they were 4.3 for the discontinuation arm and 2.7 for the continuation arm if 2 events were considered ($P = .30$; table 3).

**Incidence of secondary end points.** None of the participants had an event indicative of stage B or C of the Centers for Disease Control and Prevention HIV classification system. No participants died during the follow-up period.

**Immunologic and virologic time trends during the follow-up period.** CD4 cell counts and virus loads at the time of study entry are shown in table 1. A small but significant difference was found in CD4 cell count, and plasma virus loads were similar. During the follow-up period, no differences were present between the 2 groups as far as CD4 cell count and plasma virus load are concerned (data not shown). The CD4 cell count decreased to $\leq$200 cells/$\mu$L on 2 consecutive measurements in only 3 participants (2 in the discontinuation arm and 1 in the continuation arm); these participants were withdrawn from the study but remained in the analysis.

**DISCUSSION**

Three previous studies (2 observational studies and 1 randomized study) have been published suggesting the safety of discontinuing secondary PCP prophylaxis in HIV-infected persons whose CD4 cell counts have increased to $>200$ cells/$\mu$L after the initiation of HAART [9, 10, 12]. Our study has 2 major differences: the period of observation is longer, and 2 events were recorded. Actually, the present study shows that, in patients who discontinue secondary PCP prophylaxis, a recurrent episode of PCP is possible even when the CD4 cell count is $>200$ cells/$\mu$L. In our study, both patients had stable virological and immunological situations for $>1$ year before discontinuation of PCP prophylaxis. It is noteworthy that all studies concerning either primary or secondary PCP prophylaxis, including ours, failed to determine a CD4 cell threshold above which it could be considered safe to discontinue the prophylactic regimens.

In a study of patients with a first episode of PCP, Kaplan et al. [21] showed that patients with a CD4 cell count of $<250$ cells/$\mu$L and a CD4 cell percentage of $<14\%$ were at higher risk than were those with a CD4 cell count of $<200$ cells/$\mu$L or a history of thrush or fever; as a consequence, they suggested changing the criteria for primary PCP prophylaxis. The present study shows that, even if these criteria are considered, it could have been suggested that both patients could discontinue prophylactic regimens. In fact, the 2 events happened in patients who had CD4 cell counts of $>250$ cells/$\mu$L, and only one of these events occurred in the presence of a CD4 cell percentage of 14%. For these reasons, and because there was a lack of information about the CD4 cell percentage for all of the other participants, our study does not provide any indication regarding the threshold CD4 cell percentage or absolute CD4 cell count at which it could be considered safe to discontinue prophylactic regimens.

It is noteworthy that recurrent episodes of PCP occurring $>6$ months after the first episode, as occurred in our patients, may not represent reactivations of latent infections but may in fact be reinfections [22–25]. Moreover, in one patient, the use of systemic corticosteroids could have favored the development of PCP [26].

This randomized, controlled trial allowed us to draw some conclusions. First, despite the presence of 2 PCP episodes, the incidence of events in this study was extremely low, suggesting that it is indeed safe to discontinue secondary prophylaxis for PCP. Second, a close monitoring of CD4 cell values should be performed, and PCP prophylaxis should be reinstituted when the CD4 cell count decreases to $\leq$200 cells/$\mu$L. Furthermore, in our opinion, in the presence of previously described risk factors, such as receipt of systemic glucocorticoids treatment or antineoplastic chemotherapy, clinicians should consider reinstitution of PCP prophylaxis independent of the CD4 cell

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients who discontinued prophylaxis ($n = 69$)</th>
<th>Patients who continued prophylaxis ($n = 69$)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of follow-up, median months (IQR)</td>
<td>27.4 (24.8–29.2)</td>
<td>25.1 (20.3–28.1)</td>
<td></td>
</tr>
<tr>
<td>No. of person-years of follow-up</td>
<td>166.7</td>
<td>138.6</td>
<td></td>
</tr>
<tr>
<td>Incidence per 100 person-years (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitive cases of PCP only</td>
<td>0.6 (0.02–3.3)</td>
<td>0 (0–2.7)</td>
<td>.55</td>
</tr>
<tr>
<td>Both definitive and presumptive cases of PCP</td>
<td>1.2 (0.1–4.3)</td>
<td>0 (0–2.7)</td>
<td>.30</td>
</tr>
<tr>
<td><strong>NOTE.</strong> IQR, interquartile range.</td>
<td></td>
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</tbody>
</table>
count. Clinicians should keep in mind patient history regarding opportunistic infections, nadir CD4 cell count, and discontinuation of prophylactic regimens and maintenance therapies. In any case, patients who present with respiratory symptoms after discontinuing secondary prophylaxis should be closely evaluated for PCP even in the presence of CD4 cell counts of >200 cells/μL and complete virus load suppression.

**STUDY GROUP**

The following institutions and investigators participated in the Changes in Opportunistic Prophylaxis Study.

**Scientific Committee members.** Cristina Mussini, Alessandra Govoni, Vanni Borghi, Nicola Mongiard, Andrea Antonini, Patrizio Pezzotti, Andrea De Luca, Francesco Chiodo, Antonella d’Arminio Montorf, Lucio Bonazzi, Ercole Concia, Maria Alessandra Ursitti, Teresa Bini, Andrea Cossarizza, and Roberto Esposito.


**Acknowledgments**

We are indebted to all of the trial participants, who agreed to participate in this trial knowing that there might be a risk of acquiring opportunistic infections. Bruno De Rienzo, who started the Changes in Opportunistic Prophylaxis Study with us and is always a source of invaluable advice, is gratefully acknowledged. Antonio Cassone and Stefano Vella (Istituto Superiore di Sanità, Rome, Italy) are acknowledged for helpful discussions and continuous support. Special thanks to Judy Aberg for suggestions and English-language revision.

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