Antiretroviral Drug Use in a Cross-Sectional Population Survey in Africa: NIMH Project Accept (HPTN 043)

Jessica M. Fogel, PhD,* William Clarke, PhD,* Michal Kulich, PhD,† Estelle Piwowar-Manning, BSMT (ASCP),* Autumn Bread, MS,* Matthew T. Olson, MD,* Mark A. Marzinke, PhD,* Oliver Laeyendecker, PhD, MBA,‡§ Agnès Fiamma, MIPH,¶ Deborah Donnell, PhD,¶¶ Jessie K. K. Mbwanmo, MD,** Linda Richter, PhD,†† Glenda Gray, MBCH, FCPaeds (SA),††§§ Michael Sweat, PhD,|||

Thomas J. Coates, PhD,¶¶ and Susan H. Eshleman, MD, PhD*

Background: Antiretroviral (ARV) drug treatment benefits the treated individual and can prevent HIV transmission. We assessed ARV drug use in a community-randomized trial that evaluated the impact of behavioral interventions on HIV incidence.

Methods: Samples were collected in a cross-sectional survey after a 3-year intervention period. ARV drug testing was performed using samples from HIV-infected adults at 4 study sites (Zimbabwe; Tanzania; KwaZulu-Natal and Soweto, South Africa; survey period 2009–2011) using an assay that detects 20 ARV drugs (6 nucleoside/nucleotide reverse transcriptase inhibitors, 3 nonnucleoside reverse transcriptase inhibitors, and 9 protease inhibitors; maraviroc; raltegravir).

Results: ARV drugs were detected in 2011 (27.4%) of 7347 samples; 88.1% had 1 nonnucleoside reverse transcriptase inhibitors ± 1–2 nucleoside/nucleotide reverse transcriptase inhibitors. ARV drug detection was associated with sex (women > men), pregnancy, older age (>24 years), and study site (P < 0.0001 for all 4 variables). ARV drugs were also more frequently detected in adults who were widowed (P = 0.006) or unemployed (P = 0.02). ARV drug use was more frequent in intervention versus control communities early in the survey (P = 0.01), with a significant increase in control (P = 0.004) but not in intervention communities during the survey period. In KwaZulu-Natal, a 1% increase in ARV drug use was associated with a 0.14% absolute decrease in HIV incidence (P = 0.018).

Conclusions: This study used an objective, biomedical approach to assess ARV drug use on a population level. This analysis identified factors associated with ARV drug use and provided information on

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From the *Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD; †Department of Probability and Statistics, Faculty of Mathematics and Physics, Charles University, Prague, Czech Republic; ‡Laboratory of Immunoregulation, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Baltimore, MD; §Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; ¶Program in Global Health, University of California at Los Angeles, Los Angeles, CA; ¶¶Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA; #Department of Global Health, University of Washington, Seattle, WA; **Muhimbili University of Health and Allied Sciences, Muhimbili University Teaching Hospital, Dar es Salaam, Tanzania; ††DST-NRF Centre of Excellence in Human Development, University of the Witwatersrand, Johannesburg, South Africa; ‡‡Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, University of the Witwatersrand, Johannesburg, South Africa; §§South African Medical Research Council, Cape Town, South Africa; ||¶¶Department of Psychiatry and Behavioral Sciences, The Medical University of South Carolina, Charleston, SC; and ¶¶¶Center for World Health, David Geffen School of Medicine and UCLA Health, Los Angeles, CA.

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Correspondence to: Susan H. Eshleman, MD, PhD, Department of Pathology, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Room 646, Ross Building, Baltimore, MD 21205 (e-mail: eshleman@jhmi.edu).

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ARV drug use over time. ARV drug use was associated with lower HIV incidence at 1 study site.

Key Words: HIV, antiretroviral drug use, Africa

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INTRODUCTION

Antiretroviral treatment (ART) has health benefits for HIV-infected individuals1–3 and prevents sexual transmission of HIV in serodiscordant couples.4,5 High coverage of ART in a population can increase life expectancy6 and may lower HIV incidence.7–9 ART coverage in population studies is usually assessed using data from HIV treatment and care settings.7,10,11 This approach is limited, because some individuals may be noncompliant with their treatment regimen, and some may acquire antiretroviral (ARV) drugs from other sources.12,13 Self-report of ARV drug use has also shown to be unreliable in some research and clinic settings.14–17

ARV drug testing provides an objective biomedical measure of ARV drug use. However, large surveys of ARV drug use in populations based on ARV drug testing have been limited because of the cost and effort of traditional ARV drug testing. Our research group developed low-cost, high-throughput methods for multidrug ARV testing that have been used to assess ARV drug use in clinical trials and cohort studies.14,15,18 In this report, we evaluated ARV drug use in a large, cross-sectional survey of African adults using samples collected in the National Institute of Mental Health (NIMH) Project Accept study (HIV Prevention Trials Network 043 trial [HPTN 043]).19,20

HPTN 043 was a large multinational, phase 3, cluster randomized controlled trial in Africa and Thailand that evaluated the effect of behavioral interventions on HIV incidence at a community level.19 Control communities received standard voluntary counseling and testing. Intervention communities received enhanced community-based voluntary counseling and testing over a 3-year period (2006–2009). The intervention included community mobilization to increase testing and awareness of HIV status, accessible HIV testing in the community, and increased posttest support services.19 At the end of the intervention period, HIV incidence was assessed in a cross-sectional household survey of >50,000 adults (2009–2011).20 At the African sites, the intervention package was associated with a modest overall reduction in HIV incidence (1.52% in the intervention communities versus 1.81% in the control communities, \( P = 0.082 \)), with a significant reduction in HIV incidence among older women (\( P = 0.0085 \)).19 During the HPTN 043 trial, ART was scaled up in many resource-limited settings, including the countries where the study was conducted.10,21–24 In addition, more HIV-infected individuals became eligible for ART after 2009, when the World Health Organization raised the recommended CD4 cell count threshold for ART initiation from 200 to 350 cells per cubic millimeter.25

In this report, we used a high-throughput, qualitative, multidrug ARV assay to evaluate ARV drug use among HIV-infected adults in HPTN 043 communities in South Africa, Zimbabwe, and Tanzania.

METHODS

Study Cohort

HPTN 043 was conducted at 4 sites in Africa (Mutoko, Zimbabwe; Kisarawe, Tanzania; KwaZulu-Natal and Soweto, South Africa) and in Chiang Mai, Thailand (NCT00203749).19 Forty-eight communities (34 in Africa, 14 in Thailand) were randomized to receive either standard voluntary counseling and testing for HIV (control) or community-based voluntary counseling and testing for HIV (intervention). After the intervention period, samples were collected from eligible adults 18–32 years of age from randomly sampled households in the communities. Samples were frozen within 24 hours of sample collection. Methods used to determine HIV status and estimate HIV incidence in HPTN 043 are described in previous reports.20,26 Samples were tested in-country with HIV rapid tests. Further testing was performed at the HPTN Laboratory Center (Baltimore, MD) to determine final HIV status. HIV incidence was assessed using a multiassay algorithm that included the BED capture immunocassay, an antibody avidity assay, CD4 cell count, and HIV viral load.20 In this study, samples from HIV-infected adults from the African sites were tested for ARV drugs at the HPTN Laboratory Center. The site in Thailand had low HIV prevalence and was excluded from analyses.

Laboratory Methods

Plasma samples from HIV-infected adults were analyzed retrospectively for the presence of 20 ARV drugs, including 9 protease inhibitors (PIs; amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir), 6 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs; abacavir, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine), 3 nonnucleoside reverse transcriptase inhibitors (NNRTIs; efavirenz, nevirapine, and ritipavirine), a CCR5 receptor antagonist (maraviroc), and an integrase inhibitor (raltegravir). Briefly, 100 μL of sample and 200 μL of internal standard solution (abacavir-d4 and lopinavir-d8) were prepared using simplified solid-phase extraction on Strata-X plates. Drugs were detected using high-performance liquid chromatography (HPLC) coupled with high-resolution accurate mass spectrometry (Q Exactive; Thermo Scientific, Pittsburgh, PA). The mobile-phase system for the high-performance liquid chromatography included 10 mM ammonium acetate (aqueous phase) and 0.05% ammonium hydroxide in methanol (organic phase). Samples were introduced onto a 5 μm Hypersil Gold perfluorinated phenyl column at 100% aqueous composition and elution occurred during a 2.5-minute step-and-hold isocratic step to 100% organic phase (methanol). The mass spectrometry analysis was performed in targeted MS2 mode; fragments were detected at a resolution of 17,500 at m/z of 200. Multiplexing with a 4-channel chromatography...
system allowed for an effective analysis time of 1.5 minutes per sample. The lower limit of detection was 10 ng/mL for all 20 drugs.

Statistical Analysis
Factors associated with ARV drug use were modeled by logistic regression at subject level. The factors were adjusted for each other as well as for site, study arm, and survey period (split into 6-month intervals). Fixed community effects were included in the form of zero-sum contrasts nested within the site-by-intervention interaction. Comparison of ARV drug use in control versus intervention communities was done by a weighted paired t test performed on community-level data. The weights were proportional to harmonic means of the numbers of HIV-positive adults in the paired communities. Degrees of freedom were adjusted to take into account the unequal weights. Association of HIV incidence with ARV drug use was modeled by linear regression at the community level with ARV prevalence, site, and intervention as predictors.

Ethical Approval
The work was carried out in accordance with the Declaration of Helsinki. HPTN 043 was conducted in partnership with established community advisory boards and local government departments. Consent was obtained at the community level for trial participation. Oral consent was obtained from each participant for collection and testing of blood samples. The study was approved by participating academic institutions and ethics committees for each site.

RESULTS
Samples Used for Analysis
Blood samples were collected from adults at the 4 African sites (34 communities) during the postintervention survey. Communities were matched into pairs based on shared attributes before randomization. Samples were collected around the same time period for each community pair (Supplemental Digital Content 1, http://links.lww.com/QAI/A946). A total of 46,693 samples were collected. The sample set analyzed in this report included samples from 7354 (99.8%) of 7366 HIV-infected individuals in the trial.19,20 12 samples were not included in the analysis (7 from participants with acute/early HIV infection; 5 from participants with missing CD4 cell count data).

Detection of ARV Drugs
Results were obtained from 7347 (99.9%) of 7354 samples tested (Table 1). At least 1 ARV drug was detected in 2011 (27.4%) samples; 88.1% of those samples had 1 NNRTI with or without 1 or 2 NRTIs. In 40.3% of the samples where 1 or more ARV drug was detected, we detected a single ARV drug (81.7% NNRTI, 16.7% NRTI, 1.6% PI or raltegravir; Table 1). The most commonly detected NNRTI was efavirenz (detected in 62.3% of the samples with 1 or more ARV drug detected). Efavirenz was detected alone in 30.2% of the samples; 48.1% of those samples were from men aged 18–24 years. The most commonly detected NRTI was lamivudine (detected in 57.3% of the samples). PIs were detected in 0.8% of the samples and raltegravir (an integrase inhibitor) was detected in 0.1% of the samples; maraviroc (a CCR5 receptor antagonist) was not detected in any samples. For the analyses below, ARV drug use was defined as detection of at least 1 ARV drug.

Factors Associated With ARV Drug Use
Multivariate logistic regression analysis was used to evaluate factors associated with ARV drug use (Table 2). Several variables were independently associated with ARV drug use, as described below. Significant differences in the frequency of ARV drug use were observed at the different

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<th>TABLE 1. ARV Drugs Detected in Study Samples*</th>
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<td>Samples with ≥1 ARV drug detected, N (%)</td>
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<td>Maraviroc, N (%)</td>
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*Stored plasma samples collected from HIV-infected participants during the postintervention survey in HPTN 043 were tested for the presence of 20 ARV drugs. ARV drug use was defined as detection of at least 1 ARV drug. The table shows the number and percentage of HIV-infected study participants at each site who had at least 1 ARV drug detected in a given drug class.
†Among the samples with 1 or more ARV drug detected, 40.3% had only 1 ARV drug detected; 81.7% had NNRTI alone (91.7% had efavirenz, 8.3% had nevirapine). 16.7% had NRTI alone (56.3% had zidovudine, 22.2% had tenofovir, 10.4% had lamivudine, 8.9% had stavudine, 1.5% had emtricitabine, 0.7% had abacavir), 1.4% had a PI (100% had lopinavir), and 0.2% had raltegravir.
‡NNRTIs were detected in 90.8% of the samples that had at least 1 ARV drug detected; 62.3% had efavirenz and 29.9% had nevirapine (1% of samples had both drugs detected).
§NRTIs were detected in 65.7% of samples that had at least 1 ARV drug detected; 57.3% had lamivudine, 16.5% had stavudine, 10.7% had zidovudine, 8.3% had tenofovir, 1.0% had emtricitabine, and 0.2% had abacavir.
‖PIs were detected in 2.8% of samples with at least 1 ARV drug detected; 2.3% had lopinavir, 1.5% had ritonavir, 0.3% had darunavir, 0.1% had atazanavir, 0.1% had amprenavir, and 0.05% had saquinavir.
study sites (P < 0.0001, Table 2). The highest prevalence of ARV drug use was observed in South Africa (31.7% in Kwazulu-Natal; 25.3% in Soweto), with lower prevalence in Tanzania and Zimbabwe (21.5% and 21.3%, respectively; Table 1). ARV drug use was significantly higher in non-pregnant women than men (P < 0.0001, Table 2); ARV drugs were detected in samples from 29.4% of women (regardless of pregnancy status) and in 21.5% of men (Supplemental Digital Content 2, http://links.lww.com/QAI/A946). ARV drug use was also associated with pregnancy (P < 0.0001, Table 2). Overall, 6.7% of the women were pregnant. The prevalence of ARV drug use among pregnant women was 39.5%, with the highest prevalence in Kwazulu-Natal (58.4%) and the lowest prevalence in Zimbabwe (19%, Supplemental Digital Content 2). ARV drug use was also associated with age (P < 0.0001; Table 2). ARV drugs were detected more frequently in older adults (30.2%; aged 25–32 years) than younger adults (21.0%; aged 18–24 years) with the highest prevalence of ARV drug use among older women (33.0%, Supplemental Digital Content 2). Significant associations were also observed with marital and employment status (higher in widowed compared with married or single adults, P = 0.006; unemployed compared with employed adults, P = 0.02; Table 2). ARV drug use was not associated with CD4 cell count (27.7% for those with <350 CD4 cells/mm³ versus 27.4% for those with >350 CD4 cells/mm³3) or with socioeconomic status or education level (data not shown).

**Temporal Trends in ARV Drug Use**

ARV drug use was assessed over the course of the 28-month postintervention survey. ARV drug use increased

<table>
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<th>TABLE 2. Factors Associated With ARV Drug Use*</th>
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*ARV drug use was defined as detection of at least 1 ARV drug. The table shows results of multivariate analysis of factors associated with ARV drug use (see Methods). Additional data for the frequency of ARV drug detection in different demographic subgroups is shown in Supplemental Digital Content, Table 1. The frequency of ARV drug detection in the control and intervention arms of the study is shown in Table 3. The frequency of ARV drug detection during different 6-month intervals of the postintervention assessment is shown in Fig. 1.

†The P values summarize the overall association of the factor with ARV drug detection.

‡Period: <6 months: first 6 months of the postintervention survey period; >6 months: remainder of the postintervention survey period.

§Intervention: community-based voluntary HIV counseling and testing; control: standard voluntary HIV counseling and testing. These results refer to the first 6 months of the survey. There was no significant intervention effect after the first 6 months.

CI, confidence interval; N, number of HIV-infected participants in the subgroup; OR, odds ratio.
1.8-fold among all HIV-infected individuals during this period, from 19.7% in the first 6 months of the survey to 34.6% in the last 6 months of the survey (Fig. 1). The increase in ARV drug use over time was highest in Zimbabwe (4.3-fold) and lowest in KwaZulu-Natal (1.3-fold), and was observed in both men and women and in both younger and older adults (data not shown).

Comparison of ARV Drug Use in Control Versus Intervention Communities

The study intervention did not include assistance accessing ART or provision of ART. Study participants accessed ART using locally available services. We performed exploratory analyses to examine whether the study intervention was associated with increased ARV drug use. The prevalence of ARV drug use at the study sites ranged from 17.7% to 32.2% in the control communities and from 19.6% to 31.1% in the intervention communities (Table 3). There was no difference between ARV drug use in control versus intervention communities ($P = 0.77$; Table 3). Only Zimbabwe showed an intervention effect, with a 7.1% higher prevalence of ARV drug use in the intervention communities. The prevalence of ARV drug use was similar in the control and intervention communities for men and for women, and in both age groups (18–24 years and 25–32 years, data not shown).

ARV drug use increased during the survey period in both control communities (from 18.0% to 32.4%) and intervention communities (from 22.3% to 37.7%). In control communities, ARV use increased significantly after the first 6 months of the survey ($P = 0.004$); in contrast, the increase in ARV drug use over time in the intervention communities was not statistically significant. Prevalence of ARV drug use was higher in the intervention communities than the control communities in the first 6 months of the survey ($P = 0.01$), but not in the later period (>6 months; Table 2).

Association of HIV Incidence With ARV Drug Use

In HPTN 043, the impact of the study interventions on HIV incidence was estimated in the cross-sectional post-intervention assessment. At 3 of the 4 study sites (Zimbabwe, Tanzania, and Soweto), there was no association between ARV drug use and HIV incidence (Fig. 2). In contrast, in KwaZulu-Natal, ARV drug use was associated with lower HIV incidence (a 1% increase in ARV coverage was associated with a 0.14% absolute decrease in annual HIV incidence, $P = 0.018$). However, this association may reflect a decrease in HIV incidence over time (direct effect of the time period related to factors other than ARV drug use), rather than an effect of ART on HIV incidence. In HPTN 043, the only subgroup that had a significant decrease in HIV incidence in the intervention arm was older women (25–32 years); in this subgroup, the prevalence of ARV use was similar in the control versus intervention communities (32.5% versus 33.5%, $P = 0.61$).

DISCUSSION

We used a novel, low-cost, high-throughput, multidrug ARV assay to assess ARV drug use on a population level in a large cross-sectional survey of African adults. By testing stored plasma samples for ARV drugs, we were able to obtain an objective, biomedical measure of ARV drug use. In HPTN 043, 27% of the HIV-infected adults from the 4 African sites had at least 1 ARV drug detected in their survey sample. The prevalence of ARV drug use in this population is lower than previous estimates of ARV coverage in these countries, which were based on surveillance data from patient and pharmacy monitoring systems. According to Joint United Nations Programme on HIV/AIDS, <40% of eligible HIV-infected individuals in Zimbabwe, Tanzania, and South Africa received ART in 2009. By 2011, these estimates of ART coverage increased to 40%–59% in Tanzania and 60%–79% in Zimbabwe and South Africa. Our assessment is based on a random sample of the HIV-infected population, rather than surveillance data from known HIV-infected persons, which may account for the lower prevalence of ARV drug use in this study. Of note, the prevalence of ARV drug use in this study was slightly higher in KwaZulu-Natal (rural: 31.7%) than Soweto (urban, 25.3%).

The recommended first-line regimens at the time the study was conducted included 1 NNRTI (EFV or NVP) + 2 NRTIs (eg, 3TC + ZDV or 3TC + d4T; newer guidelines introduced during the trial included the option of 3TC + FTC or 3TC + TDF). In this study, the most (88%) of those with ARV drugs detected had an NNRTI with or without NRTIs, consistent with the recommended first-line ART regimens used in the study countries. Detection of drugs in other drug classes was rare; those drugs were not widely available and were not part of first-line ART regimens in the study countries at that time. Among the samples with any ARV drug detected,
40.3% had only 1 drug detected. Most of these individuals were probably taking multidrug regimens for treatment, with only 1 drug detected by the multidrug assay. Drugs that achieve higher levels in plasma or have longer half-lives are more likely to be detected in samples collected at random times after dosing, especially if an individual is not 100% adherent to a multidrug treatment regimen. Even if fixed-dose drug combinations were used, NNRTIs would be detected longer than NRTIs because of their longer half-lives. Some reports from Africa have noted that EFV is used for recreational purposes, which could also explain the detection of EFV in the absence of other drugs.

Detection of an NRTI alone could reflect incomplete adherence to a multidrug regimen or use of ARVs for another purpose (eg, use of 3TC for hepatitis; use of a short course NRTI regimen for postexposure prophylaxis).

Several demographic factors were strongly associated with ARV drug use in this population. ARVs were more frequently detected in samples from South Africa than Tanzania and Zimbabwe. Of note, clinic-based voluntary HIV counseling and testing services were already available as standard-of-care at the sites in South Africa at the start of HPTN 043. These services were not available at the sites in Tanzania and Zimbabwe before the study started. A study from rural Tanzania also cited higher ART coverage among older adults based on records from HIV care and treatment centers.

In this study, ARV drug use was also associated with marital status (higher in widowed compared with married or single adults) and employment status (higher in unemployed compared with employed adults). Further studies are needed to evaluate the basis for these associations.

In addition to examining demographic trends in ARV drug use, a goal of this study was to explore the association of ARV drug use and HIV incidence, the primary outcome of the HPTN 043 study. Although we did not observe an overall difference in ARV drug use in the control versus intervention communities, we did find a significantly higher prevalence of...
ARV drug use in the intervention communities during the first 6 months of the survey period (September 2009 to March 2010). This temporal pattern in intervention effect may be explained by the increases in ARV drug use that we observed in both the control and intervention communities during the survey period. These increases likely reflected both general scale-up of existing ART services through local government programs, The U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), and other organizations and the 2009 changes in World Health Organization guidelines for ART initiation, which increased the CD4 cell count threshold recommended for ART initiation. Of note, we did find a significant association between higher prevalence ARV drug use and lower HIV incidence in KwaZulu-Natal, which had both the highest prevalence of ARV drug use and the highest annual HIV incidence. At that site, a 1% increase in ARV drug use was associated with a 0.14% absolute decrease in HIV incidence; this corresponds to a 3.6% relative decline with the 3.9% annual HIV incidence observed in KwaZulu-Natal. A previous study of ART coverage in KwaZulu-Natal, based on analysis of the Hlabisa HIV Treatment and Care Programme’s database, reported that a 1% increase in ART coverage was associated with a 1.4% relative decline in HIV incidence. One limitation of our analysis is that the post-intervention survey periods in 2 of the 17 pairs of matched control and intervention communities did not completely overlap. In addition, HIV incidence was determined using a multiassay algorithm; participants who had 1 or more ARV drug detected in the survey sample were characterized as having nonrecent (prevalent) HIV infection. In conclusion, using a low-cost, high-throughput, multidrug ARV assay, we were able to assess the prevalence of ARV drug use in a large population survey, identify demographic factors associated with ARV drug use, and evaluate temporal trends in ARV drug use. We also observed an association of ARV prevalence with HIV incidence in KwaZulu-Natal, which suggest that ARV drug use could have been one of the factors contributing to reduced HIV incidence. This objective testing approach may aid other measurements of ARV drug use, such as analysis of public data sets for provision of ART or ART data provided by self-report, and may be useful in clinical trials, surveillance studies, and evaluation of public health programs using ART for HIV treatment and prevention.33

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