

Association of First-Line and Second-Line Antiretroviral Therapy Adherence

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Background. Adherence to first-line antiretroviral therapy (ART) may be an important indicator of adherence to second-line ART. Evaluating this relationship may be critical to identify patients at high risk for second-line failure, thereby exhausting their treatment options, and to intervene and improve patient outcomes.

Methods. Adolescents and adults ($n = 436$) receiving second-line ART were administered standardized questionnaires that captured demographic characteristics and assessed adherence. Optimal and suboptimal cumulative adherence were defined as percentage adherence of $\geq 90\%$ and $< 90\%$, respectively. Bivariable and multivariable binomial regression models were used to assess the prevalence of suboptimal adherence percentage by preswitch adherence status.

Results. A total of 134 of 436 (30.7%) participants reported suboptimal adherence to second-line ART. Among 322 participants who had suboptimal adherence to first-line ART, 117 (36.3%) had suboptimal adherence to second-line ART compared with 17 of 114 (14.9%) who had optimal adherence to first-line ART. Participants who had suboptimal adherence to first-line ART were more likely to have suboptimal adherence to second-line ART (adjusted prevalence ratio, 2.4; 95% confidence interval, 1.5–3.9).

Conclusions. Adherence to first-line ART is an important predictor of adherence to second-line ART. Targeted interventions should be evaluated in patients with suboptimal adherence before switching into second-line therapy to improve their outcomes.

Keywords. adherence; antiretroviral; HIV.

Global efforts towards universal access to antiretroviral therapy (ART) have led to an increase in the number of patients receiving ART in low- and middle-income countries (LMIC) [1]. Antiretroviral therapy coverage rose from approximately 3 million persons in 2007 to 9.7 million in 2012 [2, 3]. Although clinical, immunological, and virological outcomes of the human

immunodeficiency virus (HIV)-infected patients receiving first-line ART are promising [4–9], many patients are failing first-line and requiring a switch to second-line ART [10]. Approximately 6% of patients receiving first-line therapy in sub-Saharan Africa need to switch to second-line regimens in any given year [3]. For patients failing first-line ART, the World Health Organization (WHO) recommends switching from nonnucleoside reverse-transcriptase inhibitor-based regimens to protease inhibitor (PI)-based regimens. Most patients switched to second-line PI-based regimens experience good early treatment outcomes [10, 11], with undetectable viral load and increased CD4 counts after 6 and 12 months of follow-up [12, 13]. Despite treatment success in many patients on second-line ART, some patients fail relatively quickly; an estimated 33%–40% of patients receiving second-line ART are failing [14, 15], potentially due to medication nonadherence [13, 16].

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Medication nonadherence in first-line ART has been associated with stigma, food insecurity, low socioeconomic status, and long travel distances to the care sites [17–19]. Provision of free ART and decentralization of ART programs from referral hospitals to healthcare centers has been implemented in an attempt to improve adherence in many LMIC. Despite these efforts, some second-line users are still nonadherent [12, 16, 20]. Patients switched to second-line because of medication nonadherence were less likely to achieve viral suppression [21].

Due to the apparent high genetic barrier to resistance mutations in patients receiving boosted PIs [14, 22], most patients failing PI-based second-line regimens do not have PI resistance mutations, suggesting that nonadherence may be the main reason for treatment failure [14, 21, 23]. Moreover, compared with patients who switched to second-line ART due to accumulated resistant viruses, those who switched with wild-type viruses were less likely to achieve viral suppression [24]. This observation may also suggest that medication nonadherence is responsible for treatment failure among patients switched into second-line ART. Because success of second-line ART depends on high levels of adherence, these observations imply that adherence on first-line may be an important indicator of adherence to second-line ART [10, 13]. If true, targeted interventions could be implemented for these patients before switching to second-line therapy and may improve patient outcomes.

Whether individuals who were nonadherent before their switch continue to be nonadherent after switching to second-line ART is unclear. Thus, evaluating the association of adherence to first-line ART with adherence to second-line ART is critical. Furthermore, second-line ART is associated with higher costs, and second-line ART is the final salvage regimen in many LMIC, underscoring the need for evaluation [14]. We used cross-sectional survey data and linked it with prospectively collected clinical data from 5 care and treatment centers (CTCs) located in northern Tanzania to assess the effect of adherence to first-line ART on the adherence to second-line ART.

METHODS

Study Design and Population

We used a cross-sectional study design to evaluate the association of adherence to first-line ART with adherence to second-line ART. The study population consisted of HIV-infected adolescent and adult patients attending CTCs at the Kilimanjaro Christian Medical Center (KCMC), Mawenzi Regional Hospital (MRH), and Kibosho, Kilema and Machame Hospitals in Northern Tanzania between January 2004 and August 2013. According to the hierarchy of Tanzania health system, KCMC is a tertiary referral hospital, MRH is a regional hospital, and Kibosho, Kilema, and Machame serve as district hospitals. These CTCs offer treatment according to the Tanzanian Ministry of Health treatment guidelines for the provision of ART. Patients received

fixed-dose combination of stavudine, lamivudine, and nevirapine (D4T/3TC/NVP) as first-line ART. Zidovudine (AZT) and efavirenz were used in place of D4T and NVP, respectively, depending upon toxicities and concurrent medications. Each patient was seen on a monthly basis, and their prescriptions were refilled at each visit. At the time of this study, routine viral load monitoring was not available in these CTCs; therefore, patients were switched to second-line ART based on clinical and immunological criteria according to WHO Guidelines [25]. We used immunological failure criteria to identify study participants.

The drugs used for second-line ART included tenofovir (TDF), abacavir (ABC), and lopinavir/ritonavir (LPV/r); atazanavir/ritonavir was substituted for LPV/r as needed. The second-line nucleoside reverse-transcriptase inhibitor choice for adolescents and adults depended on the first-line ART. For patients on AZT or D4T in first-line ART, the default second-line option was TDF combined with 3TC or emtricitabine (FTC) and LPV/r. For those who had received TDF in first-line ART, the second-line option was an AZT-based regimen. For those who were on TDF during first-line because of intolerance to AZT or D4T, an alternative second-line option was ABC combined with 3TC or FTC and LPV/r. Patients who were less than 13 years old were excluded.

Data Collection

After obtaining informed consent, standardized questionnaires translated into Kiswahili were administered to participating patients by trained research nurses. Those who were not captured at their CTCs were interviewed by telephone. The questionnaire addressed demographic characteristics and the patient's adherence before and after switching to second-line ART. Using a visual analog scale, participating patients were asked to rate their adherence percentages before and after switching to second-line therapy.

As part of routine HIV clinical care, all patient data including demographics, medication use, opportunistic infections, adherence indicators (adherent = fewer than 2 missed days per month/nonadherent = 2 or more missed days per month), and laboratory values were collected on standardized forms, and the information was entered into a database designed and funded by Tanzanian National AIDS Control Program in collaboration with Elizabeth Glacier Pediatric AIDS Foundation. This database was searched for clinical data, and when information was missing, it was abstracted from their respective medical files. Treatment monitoring included clinical and immunological criteria; CD4 cell counts were checked at 4- to 6-month intervals using flow cytometry.

Definition of Variables

The primary endpoint was the cumulative percentage adherence to second-line ART. We defined optimal and suboptimal

adherence as percentage of self-reported cumulative adherence of $\geq 90\%$ and $< 90\%$, respectively. A cutoff of 90% was chosen for 2 reasons: first, we assessed cumulative adherence as opposed to 3-day recall, which would normally result in higher adherence percentages; and second, a previous study showed that variation in plasma viral load is not increased when adherence is between 90% and 100%; however, adherence below 90% had a significant effect in terms of plasma viral load [27]. Near perfect adherence to ART defined by adherence $\geq 95\%$ is the widely recommended minimal level of adherence for sustained viral suppression < 400 copies/mL among HIV-infected; however, the cutoff is on patients receiving unboosted PI [28]. For patients receiving boosted PI, minimal adherence of 80% is required for at least 80% of the patients to achieve viral suppression [29, 30].

The exposure of interest was the cumulative percentage adherence to first-line ART. Optimal and suboptimal adherences were defined as the percentage of self-reported cumulative adherence of $\geq 90\%$ and $< 90\%$, respectively. Other variables evaluated were age, gender, duration on first-line ART, treatment sites, CD4 cell count at the time of treatment initiation, CD4 cell count at time of switch, and the patient's weight.

Institutional review board approval was obtained from the University of KCMC.

Statistical Analyses

Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC). The distribution of continuous variables was explored to decide whether or not to categorize. Frequencies of categorical variables were calculated as the proportions of patients sampled. Crude and adjusted binomial regression models were used to assess the association of adherence to first-line ART with adherence to second-line ART. All associations were presented as adjusted prevalence ratios (APRs) with 95% confidence intervals (CIs). Estimates whose CIs excluded 1 were considered statistically significant. The final multivariate model included established demographic and clinical factors associated with adherence. Sensitivity analyses were performed with adherence redefined at 85% and 95% cutoff values.

RESULTS

From May through August 2013, 11 289 medical files were reviewed, and 656 (5.8%) identified patients who met WHO immunological failure criteria (Figure 1). Of these, 456 (69.5%) switched to second-line ART. Of those switched to second-line, 20 (4.4%) were children less than 13 years and were excluded. Among the 436 adolescent and adult patients on second-line ART, 279 (64%) were female, and 298 (68.4%) were between 30 and 55 years old (Table 1). Suboptimal adherence on first-line ART was reported by 322 (73.9%) patients. Most (351; 80.5%) had CD4 cell counts less than 200 cells/mm³ at ART initiation, and 378 (86.7%) had CD4 cell counts less than 200 cells/mm³ at

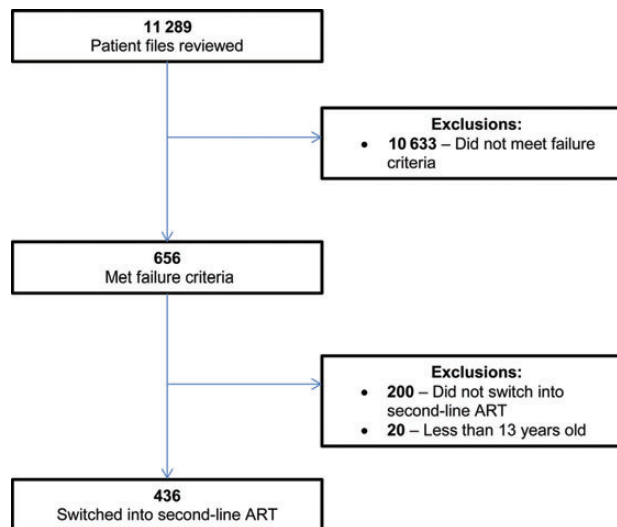


Figure 1. Study flow diagram. Selection of HIV-infected adolescents and adults receiving second-line ART at 5 infectious disease clinics in Kilimanjaro Region, Moshi, Tanzania 2004–2013. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

the time of switch. Slightly higher than half of patients (246; 54.4%) spent less than 36 months on first-line ART, and 270 (62%) came from tertiary referral hospital (KCMC) CTC. The majority (278; 63.8%) weighed between 45 kg and 70 kg. The majority of patients who had suboptimal adherence on first-line achieved optimal adherence on second-line ART (205; 63.7%).

Suboptimal Adherence

One hundred and thirty-four persons (30.7%) reported cumulative suboptimal adherence to second-line ART. Patients who had suboptimal adherence to first-line ART were much more likely to have suboptimal adherence to second-line ART than those who had optimal adherence to first-line (prevalence ratio [PR], 2.4; 95% CI, 1.5–3.9) (Table 2). In bivariable analyses, compared with patients who weighed less than 45 kg, those weighing above 70 kg were less likely to have suboptimal adherence to second-line ART (PR, 0.5; 95% CI, .3–1.0).

After adjusting for age, gender, site, duration on first-line ART, weight, baseline CD4 cell count, and the CD4 cell count at the time of switch, the effect of adherence to first-line ART on adherence to second-line ART persisted (APR, 2.4; 95% CI, 1.5–3.9) (Table 2). The effect of adherence to first-line ART on adherence to second-line ART was substantially stronger than other available factors. Several factors showed positive, but relatively imprecise, associations with suboptimal adherence to second-line ART. For example, patients switched to second-line ART at CD4 cell count less than 200 cells/mm³ were slightly more likely to report suboptimal adherence during second-line than those switched at CD4 cell count more than 200 cells/mm³ (APR, 1.2; 95% CI, .7–1.9). Compared with patients switched

Table 1. Demographic and Clinical Characteristics of HIV-Infected Adolescents Receiving Second-Line ART at 5 Infectious Disease Clinics in Kilimanjaro Region, Moshi, Tanzania, 2004–2013

Characteristics	All Patients (n = 436)	Optimal Adherence to Second-Line ART (n = 302)	Suboptimal Adherence to Second-Line ART (n = 134)
Adherence to first-line ART			
Optimal	114 (26.1)	97 (32.1)	17 (12.7)
Suboptimal	322 (73.9)	205 (67.9)	117 (87.3)
Age			
<30 years	113 (25.9)	77 (25.5)	36 (26.9)
30–55 years	298 (68.4)	207 (68.5)	91 (67.9)
>55 years	25 (5.7)	18 (6.0)	7 (5.2)
Gender			
Male	157 (36.0)	106 (35.1)	51 (38.1)
Female	279 (64.0)	196 (64.9)	83 (61.9)
Duration on first-line ART			
<36 months	246 (56.4)	172 (57.0)	74 (55.2)
36–60 months	136 (31.2)	97 (32.1)	39 (29.1)
>60 months	54 (12.4)	33 (10.9)	21 (15.7)
CD4 cell count at ART initiation			
<200 cells/mm ³	351 (80.5)	240 (79.5)	111 (82.8)
>200 cells/mm ³	85 (19.5)	62 (20.5)	23 (17.2)
CD4 cell count at time of switch			
<200 cells/mm ³	378 (86.7)	258 (85.4)	120 (89.5)
>200 cells/mm ³	58 (13.3)	44 (14.6)	14 (10.5)
Sites			
KCMC	270 (61.9)	190 (62.9)	80 (59.7)
Mawenzi	100 (22.9)	66 (21.9)	34 (25.4)
Others	66 (15.1)	46 (15.2)	20 (14.9)
Weights			
<45 kg	94 (21.5)	65 (21.5)	29 (21.6)
45–70 kg	278 (63.8)	184 (60.9)	94 (70.2)
>70 kg	64 (14.7)	53 (17.6)	11 (8.2)

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; KCMC, Kilimanjaro Christian Medical Center.

into second-line ART at less than 3 years on first-line, those switched into second-line ART after 5 years were slightly more likely to report suboptimal adherence (adjusted odds ratio, 1.2; 95% CI, .8–1.8). Patients who weighed more than 70 kg continued to be less likely to demonstrate suboptimal adherence to second-line ART (APR, 0.6; 95% CI, 0.3–1.1).

Sensitivity Analyses

When optimal and suboptimal adherence were defined as percentage of self-reported cumulative adherence of $\geq 95\%$ and $< 95\%$, respectively, patients who had suboptimal adherence to first-line ART were more likely to have suboptimal adherence to second-line ART than those who had optimal adherence to first-line ART (APR, 3.0; 95% CI, 1.7–5.2) (Table 3). Defining adherence at 85% cutoff, the effect of suboptimal adherence to

Table 2. Crude and Adjusted Risk Factors of Suboptimal Adherence to Second-Line ART Among HIV-Infected Adolescents and Adults at 5 Infectious Disease Clinics in Kilimanjaro Region, Moshi, Tanzania, 2004–2013

Variable	Bivariable Analysis Prevalence Ratio (95% CI)	Multivariable Analysis Adjusted Prevalence Ratio (95% CI)
Adherence to first-line ART		
Optimal	1	1
Suboptimal	2.4 (1.5–3.9)	2.4 (1.5–3.9)
Age		
<30 years	1	1
30–55 years	0.9 (.7–1.3)	1.1 (.7–1.5)
>55 years	0.9 (.4–1.7)	1.0 (.5–2.0)
Gender		
Male	1	1
Female	0.9 (.7–1.2)	0.9 (.7–1.2)
Duration on first-line ART		
<36 months	1	1
36–60 months	1.0 (.7–1.3)	1.0 (.7–1.3)
>60 months	1.3 (.9–1.9)	1.2 (.8–1.8)
CD4 cell count at ART initiation		
<200 cells/mm ³	1	1
>200 cells/mm ³	1.2 (.8–1.7)	0.9 (.6–1.3)
CD4 cell count at time of switch		
<200 cells/mm ³	1	1
>200 cells/mm ³	1.3 (.8–2.1)	1.2 (.7–1.9)
Sites		
KCMC	1	1
Mawenzi	1.1 (.8–1.6)	1.0 (.7–1.5)
Others	1.0 (.7–1.5)	1.0 (.6–1.5)
Weights		
<45 kg	1	1
45–70 kg	1.0 (.8–1.5)	1.0 (.6–1.5)
>70 kg	0.5 (.3–1.0)	0.6 (.3–1.1)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; KCMC, Kilimanjaro Christian Medical Center.

first-line on suboptimal adherence to second-line persisted (APR, 6.0; 95% CI, 3.0–12.2).

DISCUSSION

After increased access to ART in LMIC, a substantial proportion of patients are failing first-line ART and need a switch to second-line ART. Nonadherence to second-line ART negatively affects its potential benefits [12, 20, 24, 26]. In this study, we have shown that adherence to first-line ART is an important predictor of adherence to second-line ART among HIV-infected adolescents and adults attending 5 CTCs in Northern Tanzania. Compared with patients reporting optimal adherence to first-line ART, patients with suboptimal adherence to first-line ART were

Table 3. Sensitivity Analyses on the Effect of Adherence to First-Line on Adherence to Second-Line ART Among HIV-Infected Adolescents and Adults at 5 Infectious Disease Clinics in Kilimanjaro Region, Moshi, Tanzania, 2004–2013^a

Cutoffs	Proportion of Suboptimal Adherence to Second-Line ART (%)		Crude Prevalence Ratio (95% CI)	Adjusted Prevalence Ratio (95% CI)
	Suboptimal Adherence to First-Line ART	Optimal Adherence to First-Line ART		
85%	77 of 267 (28.8)	8 of 169 (4.7)	5.3 (2.8–9.9)	6.0 (3.08–12.2)
95%	241 of 386 (62.4)	8 of 50 (16.0)	4.0 (2.1–7.5)	3.0 (1.7–5.2)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus.

^a Models adjusted for age, gender, CD4 cell count, sites, duration on first-line ART, and weight.

2.4 times more likely to report suboptimal adherence to second-line ART.

An association between adherence to first-line and second-line ART has been reported in South Africa [21], in which the odds of >90% adherence to second-line ART was 2.5 times as high among patients whose adherence to first-line ART was above the median (67%) compared with those with first-line adherence below the median. These findings support our hypothesis that patients who are nonadherent to first-line ART are more likely to be nonadherent to second-line.

Others have made similar observations using plasma viral load as the primary endpoint. For example, 55% of patients who had subtherapeutic drug concentrations on first-line ART failed to achieve viral suppression on second-line ART [26]. Compared with patients who switched into second-line for reasons other than nonadherence, those who switched for nonadherence reasons were less likely to achieve viral suppression [10, 27]. Patients who were nonadherent on first-line likely continued to be nonadherent after switching into second-line ART, which explains treatment failure after switching.

In this study, approximately 15% of patients who had optimal adherence to first-line ART had suboptimal adherence to second-line ART. A decline of medication adherence and adherence practices over time has been reported previously [31, 32]. Although 36% of our patients who had suboptimal adherence before switching continued to have suboptimal adherence after the switch, the proportion of optimal adherence increased after switching. This result may reflect the role of current counseling efforts on the importance of regular and consistent use of medication. Using medication possession ratio as adherence assessment method, others have shown an increase in median adherence from less than 67% before switching to second-line to 92% 12 months postswitch [21].

Patients with low CD4 cell counts at the time of switch reported suboptimal adherence after switching. Low CD4 cell count values in these patients may be attributed to nonadherence before switching, and possibly these patients continued to be nonadherent after their switches. Our findings can be substantiated by previous studies demonstrating that low CD4 cell

count at the time of switch was associated with virological failure and high mortality on second-line ART [16, 33].

Approximately 30% of patients who met WHO immunological failure criteria did not switch to second-line ART. Delayed switching may be attributed to physician’s reluctance in switching patients due to the low sensitivity and positive predictive values of WHO immunological failure criteria in predicting virological failure. Delayed switching may also be due to low healthcare provider’s confidence in making switches and limited availability of treatment options. These reasons could explain why some patients did not switch to second-line ART in spite of meeting immunological failure criteria.

Our study does have a number of limitations. We used self-reported adherence to assess adherence to first- and second-line ART; however, self-reported adherence is subject to both recall bias and overestimation of adherence percentages [14, 34]. Although most patients were on first-line ART for less than 3 years, some were on treatment for more than 5 years. Because adherence assessment occurred after switching into second-line ART, recall bias is a potential concern, and misclassification could be differential (patients may have overestimated both their first-line and second-line adherence to a similar extent). If most patients overestimated their adherence percentages, patients who had suboptimal adherence to second-line would have reported optimal adherence; however, among patients who had suboptimal adherence to second-line ART, 87.3% had suboptimal adherence to first-line ART. Given high sensitivity of first-line adherence in detecting second-line adherence, it is likely that overestimation was minimal. Self-reported adherence does have limitations in accurately assessing true medication adherence. However, there is no perfect measure of medication adherence, and even plasma drug concentrations are subject to individual differences in drug metabolism, which can confuse interpretations of adherence. In addition, despite the anticipated bias and overestimations, self-reported assessment has been used extensively, and it has been shown to be associated with virological outcome [35].

Absence of plasma viral load testing certainly leads to misclassification. There may be patients regarded to have failed when in

fact they did not. There may also be patients without immunological failure who truly failed virologically, but they were not included into the study. Low CD4 cell count is more likely to predict viral failure than high CD4 cell count. Therefore, we believe minimal misclassifications might have happened in this group of patients, and they happened to a similar extent.

The study population consisted of patients who were on ART since 2004. During this time, D4T/3TC/NVP was the most common ART regimen used. Stavudine is well known to be associated with toxic effects. It is possible that some patients were poor adherent primarily because of the toxic effect related to D4T. However, depending on the toxicities, AZT was used in place of D4T.

We used a cross-sectional design to assess cumulative self-reported adherence on both first-line and second-line ART, and hence failed to account for variation of adherence over time. As noted previously, adherence and adherence practices may decline over time. For example, adherence may be high when patients are seriously ill. Regaining health may tempt people to engage in practices that may lower their adherence. Smoking and alcohol consumption are among notable practices resumed after recovery, which in turn lowered patients adherence [31]. Although 3- to 30-day recalls can produce high levels of adherence [19], reported median life-time adherence was between 60% and 62% [36, 37], suggesting change of adherence over time. The cross-sectional design of our study did not allow an assessment of the effect of adherence to first-line ART on adherence to second-line longitudinally.

The standard of care guidelines changed over the study period of 9 years. For example, different antiretroviral drugs became available over time, which could have increased their tolerability, potentially improving adherence. Such a change might result in higher adherence percentages, yet, approximately 31% of patients had second-line adherence below 90%.

CONCLUSIONS

This study reports adherence to first-line ART as an important predictor of adherence to second-line ART. Although most patients with suboptimal adherence before switch had improved adherence after switch, a substantial proportion of patients reported suboptimal adherence after switching. Patients in these CTCs are seen on a monthly basis, and adherence assessment is conducted as they come to refill their prescription. After monthly assessment, we will identify patients who report missing doses frequently and plan peer support and supervisory home-based care. Current adherence practice in these settings involves one-to-one counseling among patients with notable adherence problems. After decentralization of HIV care services, most HIV CTCs are located near patient residences. In this regard, supervisory home-based care is possible and would improve patients' adherence without causing treatment interruption

in patients with advanced disease. In addition to individual counseling, supervisory home-based care is known to improve adherence [38, 39].

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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.

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