Predictors of Suboptimal Virologic Response to Highly Active Antiretroviral Therapy Among Human Immunodeficiency Virus-Infected Adolescents:

Analyses of the Reaching for Excellence in Adolescent Care and Health (REACH) Project

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Abstract

Objective—To examine the prevalence and biopsychosocial predictors of sub-optimal virologic response to highly active antiretroviral therapy (HAART) among human immunodeficiency virus (HIV)-infected adolescents.

Design—Population-based cohort study.

Setting—Sixteen academic medical centers across thirteen cities in the United States.

Participants—One hundred and fifty four HIV-infected adolescents who presented for at least two consecutive visits after initiation of HAART.

Main Outcome Measures—Viral load (plasma concentration of HIV RNA), CD4+ T-lymphocyte count.

Results—Of the 154 adolescents enrolled in the study, 50 (32.5%) demonstrated early and sustained virologic suppression while receiving HAART. The remaining 104 adolescents (67.5%) had a poor virologic response. Adequate adherence (>50%) to HAART—reported by 70.8% of respondents—was associated with a 60% reduced odds of suboptimal virologic suppression in a multivariable logistic regression model (adjusted odds ratio = 0.4; 95% confidence interval : 0.2 – 1.0). Exposure to sub-optimal antiretroviral therapy (ART) prior to HAART, on the other hand, was associated with more than a two-fold increased odds of sub-optimal virologic response (adjusted odds ratio = 2.6; 95% confidence interval: 1.1 – 5.7).

Conclusions—Fully two-thirds of HIV-infected adolescents in the current study demonstrated a sub-optimal virologic response to HAART. Non-adherence and prior single or dual ART were associated with subsequent poor virologic responses to HAART. These predictors of HAART failure echo findings in pediatric and adult populations. Given the unique developmental stage of adolescence, age-specific interventions are indicated to address high rates of non-adherence and therapeutic failure.

Keywords

HIV; Adolescent; Antiretroviral Therapy; Highly Active; Adherence; Viral Load; CD4 Lymphocyte Count

INTRODUCTION

In 2006, adolescents aged 13 to 19 years accounted for 4% of newly diagnosed cases of human immunodeficiency virus (HIV) infection in the United States,[1] half the percentage reported in 2003.[2] Despite a decrease in the relative proportion of adolescents diagnosed with HIV, incidence rates within this age group have been steadily increasing since the late 1990s, nearly doubling between 1998 and 2006.[1] However, these data are likely to underestimate the true incidence and proportion of adolescent HIV cases, as overall incidence rate estimates were revised upward in 2008 and HIV testing coverage is much lower among adolescent compared to adult populations.[3, 4] Furthermore, the prolonged latent phase of HIV's natural history suggests a large proportion of individuals diagnosed with HIV in early adulthood were likely infected during adolescence.

Adolescents are less likely to be tested for HIV as they access health care services less frequently and with greater difficulty than their adult counterparts.[5–7] Behavioral studies have demonstrated that high-risk behaviors, lack of knowledge about HIV, and logistic impediments to accessing health systems may all contribute to delays in testing adolescents for HIV infection.[8, 9] Delays in HIV diagnosis lead to delays in treatment initiation which can result in poorer clinical outcomes. The delays to initiating care are compounded by the fact that adolescents lack adequate health insurance and do not often have access to youth-friendly clinical settings.[10, 11] These disadvantages along with complicated therapeutic regimens may predispose adolescents to poor antiretroviral therapy (ART) adherence rates that can translate into viral resistance and inadequate viral suppression.

The relationship between viral suppression and immune reconstitution in the context of highly active antiretroviral therapy (HAART) has been well documented in HIV-infected adult and pediatric populations.[12–16] Predictors of poor virologic, immunologic, and clinical outcomes have also been validated in these cohorts.[17–20] Adolescents differ in their biological and behavioral characteristics from these age groups, but are still often grouped with adults in epidemiologic studies. Given the paucity of data on HIV-infected youth populations, we sought to identify predictors of elevated viral load and decreased $CD4^+$ cell counts among adolescents on HAART.

METHODS

STUDY DESIGN

The REACH Project (Reaching for Excellence in Adolescent Care and Health) of the Adolescent Medicine HIV/AIDS Research Network is a multicenter, prospective, observational study that longitudinally evaluated prevalent HIV infections and related behavioral and biological factors in adolescents (age 12 – 19 years) for a minimum of one year (mean follow-up 2.4 years) between 1996 and 2000. This time frame allowed the

assessment of the transition from mono- and dual ART to HAART. The study cohort was restricted to participants who acquired HIV via sexual transmission or injection drug use and excluded youth infected through vertical transmission, contaminated blood products, or early childhood sexual abuse. A detailed description of the REACH study design, objectives, and procedures have been published elsewhere.[21, 22]

Participants included in the current analysis were required to meet five inclusion criteria: 1) HIV seropositive at baseline; 2) HAART naïve at baseline; 3) on HAART for at least two consecutive visits following HAART initiation; 4) documented baseline viral load; and 5) viral load available before and after HAART initiation. Approvals for the original study and subsequent analyses were obtained from all participating universities' institutional review boards. Informed consent was obtained from all participants, parents or guardians as deemed appropriate by local laws and/or university regulations.

Behavioral data were collected via face-to-face interviews, audio computer-assisted self-administered interviews, and medical record reviews. Study participants defined their race/ethnicity during direct interviews by self-identification. Interviewers measured and rated depressive signs and symptoms on the Center for Epidemiology Study Depression scale (CES-D).[23] Details of adherence assessments have been published elsewhere.[24] For the purpose of this analysis, a participant who took his/her triple antiretroviral medications as prescribed more than 50% of the time prior to a particular visit was deemed to be adequately adherent at that specific visit. If a participant then maintained adequate adherence at more than 50% of his/her visits then he/she was defined as having overall adequate adherence for the duration of the study. This definition of ART adherence deviates from standard criteria,[25] but was crafted to be more sensitive at the cost of being less specific in order to capture an adequate sample size in a population that has a high risk of non-adherence.

Host genetic factors that are collectively predictive of better immunologic control of HIV replication were captured by an algorithm that has been described previously.[26] In brief, HLA class I and CCR2/CCR5 genotypes that have a favorable impact on controlling HIV replication and/or delaying disease progression were assigned a score of +1, while unfavorable genotypes received a score of −1. At the individual level, a genetic score was calculated by summing the assigned values for all contributing HLA and CCR2/CCR5 variants within the individual. Within the study population, genetic scores ranged from −3 to +1, although individuals with extremely low scores were rare. Therefore, we collapsed -3,-2, and -1 scores into a single category of -1 for the purpose of analysis. Virologic and immunologic measures were obtained according to previously defined protocols.[21, 22]

OUTCOMES

Participants were categorized according to the magnitude and sustainability of viral load reductions while on HAART. We defined early viral responders as those who had $>1.0 \log_{10}$ viral load reduction between pre- and initial two post-HAART visits. We identified individuals as demonstrating a sustained viral response if their mean viral load from the remaining post-HAART visits was at least $0.5 \log_{10}$ lower than their pre-HAART value. Participants were ultimately classified into two categories: 1) those who had both early and sustained virologic suppression were termed "responders"; 2) those who either demonstrated early but unsustained virologic suppression or showed no early response at all were classified as "sub-optimal responders". The latter group is a composite of two types of responders because few participants (N = 15) showed an early but unsustained response. The two groups that comprised the suboptimal response categories were immunologically equivalent as measured by CD4^{+} cell count over the study's time course (data not shown). Analyses were performed using both categorization schemes. Results differed marginally

between the two analyses. Hence, we present the findings of the dichotomous categorization only.

STATISTICAL ANALYSIS

All analyses were performed using SAS Version 9.1 (SAS Institute Inc., Cary, NC). Differences in proportions of participant characteristics between the two viral response groups were assessed by chi-square test. Cochran-Mantel-Haenszel chi-square was used for ordinal categories. After determining normality assumptions to be robust, mean group differences of baseline $CD4^+$ cell count and logarithmically-transformed viral load were compared using Wilcoxon rank sum test and Student's t-test, respectively. Multivariable logistic regression models were employed to examine the relationship between viral response and baseline age, race/ethnicity, and all dichotomous variables. Magnitudes of association are reported as adjusted odds ratios (OR) and 95% confidence interval (CI) for each covariate in the model.

Mean $\log_{10}$ viral load and $CD4^+$ cell counts were calculated for pre- and post-HAART visits across the two responder groups. The pre-post HAART differences between the two groups were compared using Student's t-test. Changes in viral load across all time points were examined using longitudinal data analytic methods. Specifically, we estimated changes in $\log_{10}$ viral load within participants and between responder groups using a mixed linear model for repeated measures. Model-selection strategies were used and baseline age, sex and race/ethnicity were adjusted for potential confounding. Variance-covariance structure and model fit diagnostics were assessed for each model.

RESULTS

Of the 154 adolescents included in the study, most were black (72.7%), female (73.4%), and between the ages of 17 and 19 years (70.8%) at enrollment (Table 1). Nearly half (49.4%) of the participants were depressed as assessed by the CES-D scale. More than two-thirds (68.4%) of adolescents reported ever having used alcohol. Of those, 83 (79.8%) reported alcohol use in the three months prior to interview. Illicit drug use was even more prevalent (83.6%). Seventy-three (47.4%) adolescents had a history of using mono- or dual ART before commencing HAART. More than one hundred participants (70.8%) met our definition of medication adherence during the course of follow-up.

According to the Centers for Disease Control and Prevention HIV staging system,[27] 58 (37.7%) adolescents met clinical criteria for early HIV disease, 65 (42.2%) were at the intermediate stage of infection, and 31 (20.1%) were at the late stage of their disease course. The mean baseline viral load of the study population was 3.93 $\log_{10}$ copies/mL (standard deviation (SD), 0.88) while the mean $CD4^+$ cell count was 495 cells/µL (SD, 248). Fifty (32.5%) adolescents demonstrated early and sustained viral suppression ("responders") while 15 (9.7%) had an early but unsustained viral load reduction and 89 (57.8%) showed little or no viral response at all while on HAART. The latter two groups comprised the "sub-optimal responders".

When we compared individuals according to virologic response to HAART, we found no differences in age, sex, race, education, evidence of depression, or history of drug use. Clinical stage of disease progression, immunogenetic profile, baseline $CD4^+$ cell count, and viral load values were also similar across groups. However, responders had a higher proportion of individuals who reported ever using alcohol than sub-optimal responders (80.0% vs. 61.5%, P = .03). Adherence rates and prior use of mono- or dual ART also differed by virologic response. Responders were less likely to have had a prior history of ART use than sub-optimal responders (30.0% vs. 55.8%, P = .003). Also, responders had

been significantly more adherent to their HAART regimen when compared to sub-optimal responders (82.0% vs. 65.3%, $P = .03$).

Despite statistically significant differences between groups on three separate parameters, only prior ART use was still significantly associated with sub-optimal virologic response on multivariable logistic regression modeling (adjusted OR, 2.6; 95% CI, 1.1–5.7) (Table 2). There was also a strong trend toward protection from sub-optimal virologic response with adequate HAART adherence (OR, 0.4; 95% CI, 0.2–1.0). Comparisons between HAART response groups revealed that mean pre-HAART plasma concentration of HIV RNA was 0.36 $\log_{10}$ copies/mL higher in the responders (4.13 $\log_{10}$ copies/mL; SD, 0.76) compared to sub-optimal responders (3.77 $\log_{10}$ copies/mL; SD, 0.90) ($P < .001$) (Table 3). At post HAART visits, viral responders had a 7-fold $\log_{10}$ copies/mL viral load decrement compared to sub-optimal responders (−2.11 log10 copies/mL; standard deviation (SD), 0.68 vs.−0.29 $\log_{10}$ copies/mL; SD, 0.93; $.P < .001$) (Figure 1). And the responders maintained at least 1.0 $\log_{10}$ copies/mL lower concentration of plasma HIV RNA than sub-optimal responders on all subsequent post-HAART initiation visits except the last ($P < .001$). After the baseline visit at which the responders had a lower CD4+ cell count than the sub-optimal response group (458 cells/μL vs 503 cells/μL, $P .03$), the responders consistently exhibited significantly higher CD4+ cell counts across all remaining visits ($P < .001$).

COMMENT

Data on the predictors of clinical outcomes in HIV-infected adolescents are sparse and primarily limited to long-term survivors of perinatal transmission.[28, 29] Since adolescents with HIV infection may not know their status and/or may not be in clinical care, it is hard for any single site outside of Africa to have a large enough number of HIV-infected adolescents to tease out the factors salient to clinical failure. The REACH project made it possible for us to overcome these limitations by combining 16 sites from 13 diverse locales in US cities for a prospective care-based epidemiologic study.

We found that adolescents with a prior history of ART use were more than twice as likely to have a sub-optimal virologic response to HAART than if they had been completely ART naïve. These outcomes are consistent with previous studies in both adults and children. Use of mono- or dual therapy is inherently sub-optimal and precipitates the emergence of resistant HIV strains. We acknowledge the possibility that adolescents on prior ART may have been non-adherent with their medication regimen as well. We found, however, that adolescents with at least 50% adherence to their HAART regimen through at least 50% of their study visits were 60% less likely to exhibit a poor virologic response. That even modest ART adherence should have had such a large protective effect is encouraging. Still, moderate adherence poses a high risk for emergence of viral resistance as it is well established that the lower the proportion of adherent participants, the higher the mean viral load.[30, 31] Most studies have indicated that exceptionally high adherence (>95%) is needed in order to maintain adequate virologic suppression.[32–34] These results are, therefore, consistent with findings from studies in both adults and children that show HAART adherence is essential to achieve sustained suppression of HIV replication and immunologic reconstitution, although an elevated risk of developing resistant viral strains remains.[35–37]

Despite the consistency of our results with prior studies in adult and pediatric populations, our study had several limitations. Adherence data that are based on self-report are subject to imprecision and recall bias. To reduce such bias, REACH study interviews were conducted in a uniform fashion, making a differential bias between the two outcome groups less likely. We also used less rigorous criteria for the definition of adherence. That better adherence should have been highly protective against both viral load increments and CD4+ cell count

decrements suggests that a stricter definition of adherence would not necessarily have changed our findings (though it would have reduced our statistical power as excellent adherence was rare in this population). Also, we only assessed adherence to HAART; adherence to any prior antiretroviral use was not considered. Compared to other adult cohorts, our study's sample size was much smaller. However, the current study is one of the largest analyses of an HIV-infected adolescent population, drawing upon a geographically diverse set of sites across the US. Finally, due to cost restraints, we were not able to perform resistance genotyping or phenotyping on study participants

HIV-infected youth have many special needs in coping with their disease.[38] While we found that predictors of virologic failure in adolescents are similar to those in children and adults, adolescent psychosocial issues must be addressed to ensure clinical success. Many adolescents live at home and may not reveal their status to parents and guardians who are then unable to provide assistance in adhering to therapy.[39, 40] Other youth not living with parents or guardians may have transient housing arrangements or may be living on the street that complicate adequate adherence as housing, food, and shelter often take precedence over medication adherence.[41, 42] Furthermore, even when treatment is sought, additional barriers related to availability, acceptability, and equity of services make adherence difficult.

Adherence to HAART will require youth friendly clinical settings and social support through community outreach efforts.[9, 43] The adolescent population is in a unique transition state from child to adulthood; this requires tailored services to ensure proper adherence. Our data add support for increased focus on adherence support services for HIV-infected adolescents, particularly as fully two-thirds of youth failed to have an adequate virologic response to HAART. The strong association observed in this study between better adherence and both early and sustained virologic responses among adolescents suggests an urgent need to maximize supportive adherence programs in the context of the broader social needs of HIV-infected youth.

Acknowledgments

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A. Mean pre-HAART and post-HAART logvl by two viral response groups
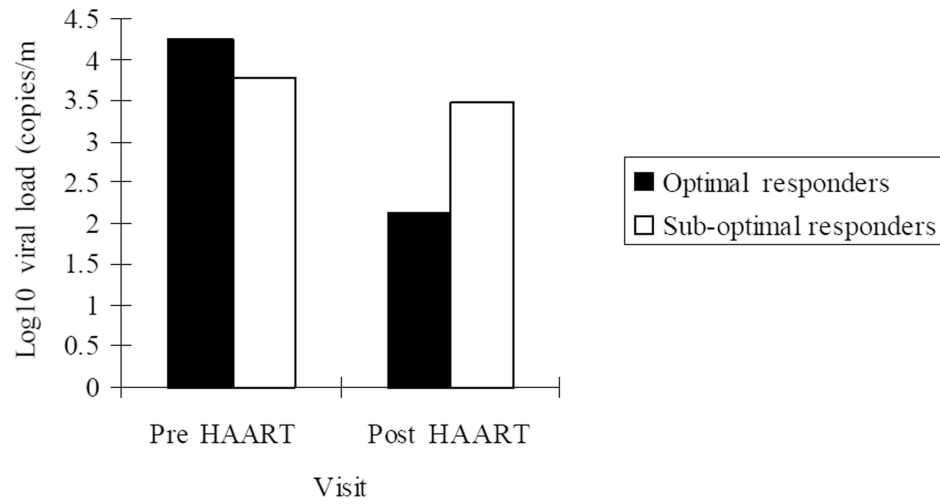
B. Mean pre-HAART and post-HAART CD4+ cell count by two viral response groups
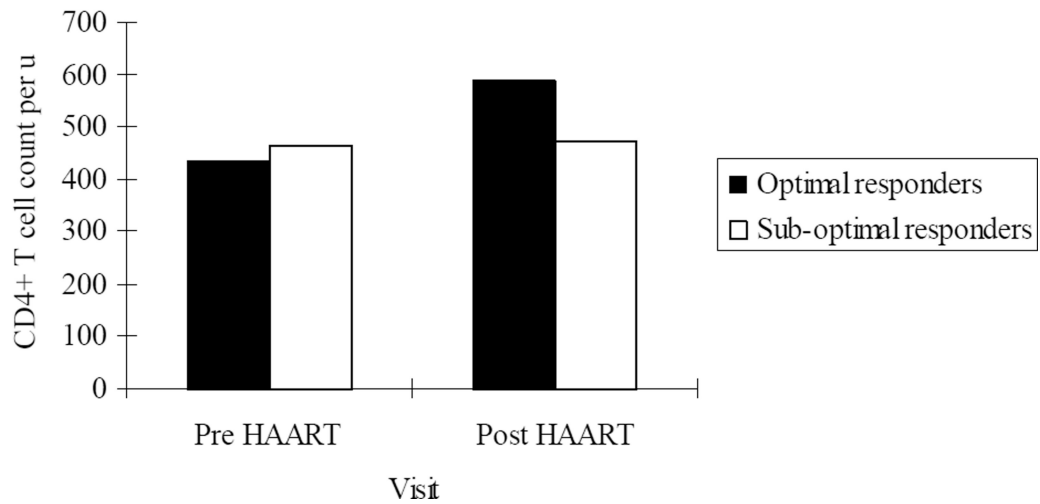
Figure 1.
Pre-Post HAART Viral Load and CD4+ Cell Counts According to Virologic Response

Table 1

Baseline Characteristics of 154 HIV-Infected Adolescents According to Virologic Response to HAART

	Responders[b] (N = 50) (%)	Sub-Optimal Responders (N = 104) (%)	P
Age, years			
12 – 16	28.0	29.8	.80
17 – 19	72.0	70.2	
Sociodemographic characteristics			
Sex, female	68.0	76.0	.30
Race, black	64.0	76.9	.09
School drop-out	20.0	26.9	.40
Ever used alcohol	80.0	61.5	.03
Used alcohol in last 3 months	62.0	50.0	.60
Ever used illicit drugs	84.0	67.3	.40
Used illicit drugs in last 3 months	68.0	55.7	.70
Depressed[c]	52.0	48.1	.60
Clinical characteristics			
Prior history of ART use	30.0	55.8	.003
Adequate HAART Adherence	82.0	65.3	.03
HIV clinical stage[d]			
Early	44.0	34.6	.50
Intermediate	38.0	44.2	
Late	18.0	21.0	
Baseline laboratory measures, mean (SD)			
CD4+ T cell count per μl	477 (219)	504 (262)	.54
Log_{10} HIV RNA copies/mL	4.05 (0.73)	3.87 (0.94)	.20
Immunogenetic score[e]			
−1	32.0	36.5	.76
0	60.0	52.8	
1	6.0	7.7	

Abbreviations: HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; ART, antiretroviral therapy; SD, standard deviation

[a]*P* values were calculated by Pearson chi-square test and Fisher's exact test for categorical variables and Student's or Wilcoxon rank sum t-test for continuous variables

[b]Responders had a >1.0 log_{10} plasma HIV RNA copies/mL reduction between pre-HAART and the initial two post-HAART visits as well as >0.5 log_{10} reduction between pre-HAART and the mean of all post-HAART visits.

[c]Measured according to the Center for Epidemiology Study Depression scale.[23]

[d]Stage of disease progression is defined according to the revised Centers for Disease Control and Prevention classification scheme.[27]

[e]Immunogenetic score was calculated according to an algorithm describe previously.[26]

Table 2

Multivariable Adjusted Likelihood of Sub-Optimal Virologic Response to HAART in Association with Sociodemographic Characteristics Among 154 HIV-Infected Adolescents.[a,b]

	Unadjusted OR	Adjusted OR (95% CI)
Age, 17 – 19 years	0.9	0.9 (0.4–2.2)
Sex, male	0.7	1.0 (0.4–2.3)
Race, black	1.9	1.8 (0.8–4.2)
Depressed [c]	0.9	1.0 (0.5–2.2)
Ever used alcohol	0.4	0.4 (0.1–2.3)
Ever used illicit drugs	0.6	1.4 (0.2–10.1)
Prior history of ART use	2.9	2.6 (1.1–5.7)
Adequate HAART Adherence	0.4	0.4 (0.2–1.0)
Immunogenetic score, 0 or 1 [d]	0.9	0.8 (0.4–1.8)

Abbreviations: HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; ART, antiretroviral therapy; OR, odds ratio; CI, confidence interval

[a]Responders had a >1.0 $\log_{10}$ plasma HIV RNA copies/mL reduction between pre-HAART and the initial two post-HAART visits as well as >0.5 $\log_{10}$ reduction between pre-HAART and the mean of all post-HAART visits.

[b]Variables with univariate *P* values .2 were included in the multivariable logistic regression model. ORs and 95% CIs were calculated before removal from a backward elimination model.

[c]Measured according to the Center for Epidemiology Study Depression scale.[23]

[d]Immunogenetic score was calculated according to an algorithm describe previously.[26]

Table 3

Mixed Model of Plasma Concentrations of HIV RNA and CD4^{+} Cell Counts Among Adolescent Responders and Sub-Optimal Responders to HAART Before and After HAART initiation. [a, b]

	Pre-HAART	Post-HAART						
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	P
Log$_{10}$ HIV RNA [c]								
Response	4.13 (0.76)	2.14 (0.69)	2.28 (1.04)	2.44 (1.02)	2.54 (1.05)	2.73 (1.06)	2.85 (1.05)	<.001
Sub-optimal response	3.77 (0.90)	3.49 (1.14)	3.79 (1.05)	3.65 (1.16)	3.71 (1.13)	3.86 (1.16)	3.59 (1.22)	
CD4^{+} cell count [c]								
Response	458 (224)	586 (263)	577 (254)	600 (272)	624 (272)	626 (284)	628 (331)	<.001
Sub-optimal response	503 (218)	464 (253)	483 (257)	505 (315)	465 (259)	461 (276)	466 (260)	
HAART adherence [d]								
Response	----------	40 (80.0)	31 (62.0)	37 (74.0)	30 (62.5)	27 (65.9)	22 (57.9)	<.001
Sub-optimal response	----------	62 (59.6)	55 (52.9)	53 (54.1)	43 (45.7)	40 (45.5)	45 (53.6)	

Abbreviations: HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy.

[a] The time between each visit was 3 months.

[b] Responders had a >1.0 log10 plasma HIV RNA copies/mL reduction between pre-HAART and the initial two post-HAART visits as well as >0.5 log10 reduction between pre-HAART and the mean of all post-HAART visits.

[b] Data are mean (standard deviation), unless otherwise indicated.

[c] Log10 HIV RNA - copies/mL; CD4+ cell count - cells/μL.

[d] Participants were adherent to HAART at each visit if they reported taking there making medications 50% of the time.