Five-Year Mortality for Adults Entering Human Immunodeficiency Virus Care Under Universal Early Treatment Compared With the General US Population

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Background. Mortality among adults with human immunodeficiency virus (HIV) remains elevated over those in the US general population, even in the years after entry into HIV care. We explore whether the elevation in 5-year mortality would have persisted if all adults with HIV had initiated antiretroviral therapy within 3 months of entering care.

Methods. Among 82 766 adults entering HIV care at North American AIDS Cohort Collaboration clinical sites in the United States, we computed mortality over 5 years since entry into HIV care under observed treatment patterns. We then used inverse probability weights to estimate mortality under universal early treatment. To compare mortality with those for similar individuals in the general population, we used National Center for Health Statistics data to construct a cohort representing the subset of the US population matched to study participants on key characteristics.

Results. For the entire study period (1999–2017), the 5-year mortality among adults with HIV was 7.9% (95% confidence interval [CI]: 7.6%–8.2%) higher than expected based on the US general population. Under universal early treatment, the elevation in mortality for people with HIV would have been 7.2% (95% CI: 5.8%–8.6%). In the most recent calendar period examined (2011–2017), the elevation in mortality for people with HIV was 2.6% (95% CI: 2.0%–3.3%) under observed treatment patterns and 2.1% (.0%–4.2%) under universal early treatment.

Conclusions. Expanding early treatment may modestly reduce, but not eliminate, the elevation in mortality for people with HIV.

Keywords. HIV; antiretroviral therapy; mortality; cohort studies.

While the survival outlook for someone newly diagnosed with human immunodeficiency virus (HIV) was dismal in the 1980s and early 1990s, new classes of antiretroviral drugs, improved medical care, and updated public health guidelines have dramatically improved survival for people with HIV. Decades of randomized trials and observational studies have documented significant reductions in mortality after initiation of new treatments and rollout of new treatment guidelines [1–3]. However, mortality rates among people with HIV remains elevated above those in the general US population, even after entry into HIV care [4].

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The underlying factors driving this lingering elevation in mortality are unknown and likely multifactorial. Even in the "test-and-treat" era, delays in presentation to care [5], delays in antiretroviral treatment (ART) initiation [6], and losses to clinical follow-up persist [7–10]. Moreover, existing medications are imperfect and may have uncertain safety with long-term use [11, 12]. In addition, there are shared structural and behavioral factors that increase the risk of both HIV acquisition and mortality [13], and people with HIV may also be living with other chronic conditions that are associated with increased mortality rates [14–17].

In the current study, we examined whether the remaining elevation in 5-year mortality among adults with HIV, compared with the US population, would have persisted under modern universal early treatment initiation. Specifically, we compared 5-year mortality among 82 766 adults entering HIV care at a North American AIDS Cohort Collaboration (NA-ACCORD) clinical site in the United States under a hypothetical intervention on treatment timing with the expected 5-year mortality

among these individuals if they had the same covariate-specific mortality risk as the US population, with the expected risk computed using aggregate data from the National Center for Health Statistics (NCHS). Quantifying the elevation in mortality that remains after universal early treatment can inform efforts to improve care for people with HIV.

METHODS

Data Sources

US Population and Mortality Data

We obtained data on the 47 812 945 deaths occurring in the United States from 1999 to 2017, using the NCHS detailed mortality files. We aggregated the number of deaths for each year by age (year), sex (male/female), race (white, black, American Indian, or Asian/Pacific Islander), ethnicity (Hispanic/non-Hispanic), and county of residence. We merged the mortality data with census data provided by the NCHS describing the estimated population size in each of the strata defined above for all US counties over the relevant time period. These merged data, containing both the number of deaths and population size by year, age, sex, race, ethnicity, and county of residence, composed our "US population and mortality" data set.

HIV Cohort Data

Data on adults with HIV in the United States were obtained from the NA-ACCORD [18], which includes 29 contributing single and multisite clinical and interval epidemiologic cohorts of HIV-seropositive participants that encompass many longitudinal HIV/AIDS cohort studies in the United States and Canada and has demonstrated that the demographic characteristics of its US participants are similar to those of individuals receiving new HIV diagnoses in the United States, as captured by the US Centers for Disease Control and Prevention's HIV surveillance system [19, 20].

Participants were enrolled in NA-ACCORD contributing cohorts if written informed consent or a waiver of consent was obtained; research activities involving human subjects have been approved by each cohort's local institutional review board and the Johns Hopkins School of Medicine. Data are collected according to individual cohort protocol, harmonized by the NA-ACCORD Data Management Core (Washington University, Seattle), and assembled into analysis data files by the NA-ACCORD Epidemiology/Biostatistics Core (Johns Hopkins University, Baltimore, Maryland). NA-ACCORD enrollment criteria include successful linkage to care, defined as a ≥2 HIV care visits within 12 months. Participants are observed to disengage and reengage in care after linkage. For this analysis, we included data from US cohorts that contribute data collected through routine clinical HIV care. Interval cohorts were excluded so that results characterized patients actively in care. Data-driven cohort open and close dates for each participating cohort, established by NA-ACCORD after reviewing core data (eg, dates of death, biomarker measurements, and ART prescriptions), are shown in Supplementary Figure 1 [21].

Covariates for the current analysis included age at entry into NA-ACCORD, birth sex, race/ethnicity, zip code, CD4 cell count at NA-ACCORD enrollment, and HIV transmission risk factors. We harmonized covariate data between NA-ACCORD and NCHS data by collapsing race and ethnicity into a single measure, including the categories non-Hispanic white, non-Hispanic black, non-Hispanic Asian, non-Hispanic American Indian/Alaska native, and Hispanic.

In NA-ACCORD, place of residence was provided using 3- or 5-digit zip codes rather than counties. To cohere with the population and mortality data for the general population, we mapped 5-digit zip codes to counties using zip code to county crosswalk tables provided by the US Department of Housing and Urban Development [22]. When only 3-digit zip codes were provided, we mapped the 3-digit zip code to a list of possible counties using the same crosswalk tables. We excluded 1 cohort that did not provide data on zip code of residence.

Mortality data, including dates of death, for participants in NA-ACCORD were obtained through regular queries to the Social Security Death Index, the National Death Index, or state vital statistics registries. Dates of death were imputed for decedents with missing information on day or month of death (on the 15th day or 6th month of the year, respectively). Dates of first ART ("treatment") and clinic visits were abstracted from clinical records.

For our analysis, we identified 90 639 patients aged ≥18 years of age who newly enrolled in HIV care at NA-ACCORD clinical cohort sites in the United States during or after 1999. We identified patients who were newly enrolled in care as those who did not have a recorded date of treatment initiation or AIDS diagnosis before cohort enrollment date or a suppressed viral load (<75 copies/mL) measured between 30 days before and 7 days after date of entry into care. We excluded 3 intersex patients who could not be matched to the US population data, 7833 patients (8.6%) with missing data on covariates, including race/ethnicity (n = 4687) and/or zip code at study entry (n = 3376), and 34 patients with unknown years of death, for a final analytic sample of 82 766 patients (Supplementary Figure 2). We assessed the sensitivity of our results to these exclusions by comparing overall mortality risks before and after excluding those with missing covariate data.

Statistical Methods

To estimate 5-year mortality risks, patients were observed from NA-ACCORD enrollment (occurring after the cohort open date and 1 January 1999), until whichever of the following occurred first: death, loss to follow-up, administrative censoring 5 years after study entry, the cohort close date, or 31 December 2017. Patients were considered lost to follow-up on the date when they had had a 12-month gap between clinic visits at an

NA-ACCORD site [23]. In supplemental analyses, we censored participants on the date when they had an 18-month gap in care to assess the robustness of findings to our definition of loss to follow-up.

We compared 5-year mortality between (1) adults entering HIV care under their observed treatment patterns; (2) adults entering HIV care had they, possibly contrary to fact, started treatment within 3 months of entry into care (universal early treatment); and (3) this set of patients had they been subject to the same age-, sex-, race/ethnicity-, and county-specific mortality rates as the US population (expected mortality).

We estimated the 5-year mortality (ie, the cumulative risk [24] of death 5 years after entry into care) among those entering HIV care under observed treatment patterns using the complement of the Kaplan-Meier estimator of the survival function [25]. We applied stabilized inverse probability of censoring weights to account for informative censoring [26]. We included covariates thought to be associated with censoring and mortality including age, sex, race/ethnicity, site, self-reported HIV transmission risk factors, and time-varying CD4 cell count and $\log_{10}$ HIV viral load in the weights. Age, CD4 cell count, and HIV viral load were included as continuous variables, modeled using restricted quadratic splines [27].

To estimate mortality among people entering care for HIV had they experienced "early" treatment, we additionally censored patients at 3 months if they had not yet started treatment. To compute mortality under this treatment plan, we applied both the standard inverse probability of censoring weights to account for informative loss to follow-up and a second weight to account for preferential early treatment of certain types of patients. The purpose of this approach was to weight participants remaining in the data set at each time point to have the same distribution of baseline and time-varying covariates as those in the target population (ie, all adults entering care for HIV at a US clinical NA-ACCORD site, irrespective of ART timing). We included the covariates listed above in the treatment weights, because these variables were thought to be associated with both treatment timing and mortality. We estimated 5-year mortality under universal early treatment using the complement of the weighted Kaplan-Meier estimator, and we computed 95% confidence intervals (CIs) around weighted mortality estimates using robust standard errors. Details are provided in Appendix 1.

We estimated expected mortality among eligible patients (had they experienced the same age-, sex-, race/ethnicity-, and county-specific mortality as the general US population) using the approach previously described by Edwards et al [4]. Briefly, we created a population-based synthetic cohort [28] of people in the United States of the same age in the same year, matched to each eligible participant starting care at an NA-ACCORD site for sex, race/ethnicity, and county of residence, using the NCHS data. We computed the mortality in each synthetic cohort, using the Kaplan-Meier estimator, and averaged mortality risk functions across all synthetic cohorts to estimate the overall expected mortality risk function among eligible people in NA-ACCORD (Appendix 2).

We stratified the estimates of 5-year mortality risks by calendar period of entry into HIV care: 1999–2004, 2005–2010, and 2011–2017. We also estimated risk differences overall and by calendar period, comparing 5-year mortality risks among those entering care for HIV (both under the treatment patterns observed and universal early treatment) with those in the US population. Standard errors and 95% CIs for the risk differences were obtained using the delta method [29].

RESULTS

Overall, 82 766 eligible adults entered care for HIV at a participating NA-ACCORD clinical site between 1999 and 2017. Nearly half (46%) were non-Hispanic black, 35% were non-Hispanic white, and 16% were Hispanic (Table 1). The majority of patients were between the ages of 35 and 54 year at entry into care (57%), and most patients were male (84%).

Where measured, the median CD4 cell count at study entry increased from 284/μL (interquartile range, 105–479/μL) among patients entering NA-ACCORD between 1999 and 2004 to 366/μL (175–558/μL) among those entering between 2011 and 2017. The probability of starting treatment in the first 3 months after entering HIV care rose over time from 41% among those entering care between 1999 and 2004 to 71% among those entering care between 2011 and 2017 (Figure 1). Treatment regimens also shifted over time, with nearly all treated patients starting protease inhibitors or nonnucleoside reverse-transcriptase inhibitors in the first calendar period and nearly 40% starting an integrase inhibitor–containing regimen by the most recent calendar period (Supplementary Figure 3).

Among adults entering care for HIV, the 5-year mortality risk while in care was 10.9% under the observed patterns of treatment and 10.1% under universal early treatment. In the matched US population, the 5-year mortality risk was 2.9% (Table 2). Over calendar time, 5-year mortality risks among adults entering care for HIV dropped dramatically, both under observed treatment patterns and under universal early treatment, while 5-year mortality risks in the matched US population declined only slightly (Supplementary Figure 4).

The overall mortality risk difference (quantifying the gap in 5-year mortality risks between adults in care for HIV and the matched US population) was smaller under universal early treatment (difference, 7.2% [95% CI: 5.8%–8.6%]) than under the observed treatment patterns (7.9% [7.6%–8.2%]) (Figure 2). Mortality risk differences between adults in care for HIV and the matched US population declined over time, such that, in the most recent calendar period from 2011 to 2017, adults entering care for HIV were only 2.6% (95% CI: 2.0%–3.3%) more likely to die within the first 5 years of HIV

Table 1. Characteristics of 82 766 Eligible Patients Entering Care for Human Immunodeficiency Virus Between 1999 and 2017, Stratified by Calendar Period at Entry into Care

Characteristic	Patients, No. (%)			
	Overall	Entered Care in 1999–2004	Entered Care in 2005–2010	Entered Care in 2011–2017
Race/ethnicity				
NH white	29 084 (35.1)	11 994 (36.8)	9099 (33.6)	7991 (34.6)
NH black	38 263 (46.2)	15 133 (46.4)	12 854 (47.4)	10 276 (44.5)
NH American Indian	350 (0.4)	131 (0.4)	118 (0.4)	101 (0.4)
NH Asian/Pacific Islander	1463 (1.8)	379 (1.2)	468 (1.7)	616 (2.7)
Hispanic	13 606 (16.4)	4951 (15.2)	4565 (16.8)	4090 (17.7)
Age at study entry				
18–34	23 169 (28.0)	7219 (22.2)	7564 (27.9)	8386 (36.3)
35–54	47 067 (56.9)	21 261 (65.2)	15 221 (56.2)	10 585 (45.9)
≥55	12 530 (15.1)	4108 (12.6)	4319 (15.9)	4103 (17.8)
Sex				
Female	13 448 (16.2)	5412 (16.6)	4674 (17.2)	3362 (14.6)
Male	69 318 (83.8)	27 176 (83.4)	22 430 (82.8)	19 712 (85.4)
US region of residence[a]				
Northeast and mid-Atlantic	29 016 (35.1)	11 018 (33.8)	9458 (34.9)	8540 (37.0)
South	27 909 (33.7)	10 591 (32.5)	9540 (35.2)	7778 (33.7)
Midwest and North Central	5332 (6.4)	2844 (8.7)	1471 (5.4)	1017 (4.4)
West	20 509 (24.8)	8135 (25.0)	6635 (24.5)	5739 (24.9)
CD4 cell count at entry into NA-ACCORD, cells/μL[b]				
≥750	4483 (5.4)	1396 (4.3)	1463 (5.4)	1624 (7.0)
500–749	9250 (11.2)	2941 (9.0)	3171 (11.7)	3138 (13.6)
350–499	10 047 (12.1)	3296 (10.1)	3601 (13.3)	315 (13.7)
200–349	11 083 (13.4)	4030 (12.4)	4020 (14.8)	3033 (13.1)
<200	17 552 (21.2)	7139 (21.9)	6242 (23.0)	4171 (18.1)
Missing	30 351 (36.7)	13 786 (42.3)	8607 (31.8)	7958 (34.5)
Self-reported HIV transmission risk category[c]				
MSM	28 782 (34.8)	8573 (26.3)	9599 (35.4)	10 610 (46.0)
IDU	14 746 (17.8)	8279 (25.4)	4218 (15.6)	2249 (9.7)
Other	41 192 (49.8)	16 495 (50.6)	13 909 (51.3)	10 788 (46.8)

Abbreviations: HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design; NH, non-Hispanic.

[a]The region of residence was categorized by the first digit of the zip code, such that those beginning with 0, 1, or 2 were labeled "Northeast or mid-Atlantic," those beginning with 3 or 7 were labeled "South," those beginning with 4, 5, or 6 were labeled "Midwest and North Central," and those beginning with 8 or 9 were labeled "West."

[b]The baseline CD4 cell count was defined as the last count measured between 30 days before and 14 days after a participant's enrollment date.

[c]Self-reported transmission risk category. These categories were not mutually exclusive (ie, some participants appear in both MSM and IDU rows). The "Other" category includes those self-reporting neither MSM nor IDU risk factors but reporting heterosexual transmission, blood transfusions, laboratory or medical settings, other risk factors, or unknown transmission route.

care than matched individuals in the US population. Under the universal early treatment intervention, the mortality risk difference between those entering HIV care and the matched US population in the most recent period was 2.1% (95% CI: −.0% to 4.2%). Results were similar when censoring at 18, rather than 12, months without a clinic visit (Supplementary Table 1), and overall mortality results were similar when analyses were not restricted to those with complete covariate data (Supplementary Table 2).

DISCUSSION

We assessed the extent to which a strategy to provide universal early ART to adults entering HIV care would reduce the elevation in mortality rates observed among adults with HIV, compared with the US population. We estimated that early treatment appeared to reduce, but not eliminate, this elevation in 5-year mortality over the 5 years after entry into HIV care. In the most recent calendar period examined (2011–2017), we estimated that early treatment reduced the elevation in mortality by about 20%: from a 2.6% 5-year mortality risk difference under observed treatment patterns to a 2.1% difference under universal early treatment.

Existing work has shown that people with HIV have higher mortality risks and shorter life expectancy than the US population [4, 17, 30–32], and that early ART is effective in improving survival [1, 2, 30, 33, 34]. We estimated that universal treatment within the first 3 months of care would result in a modest reduction in 5-year mortality risk. This reduction was likely

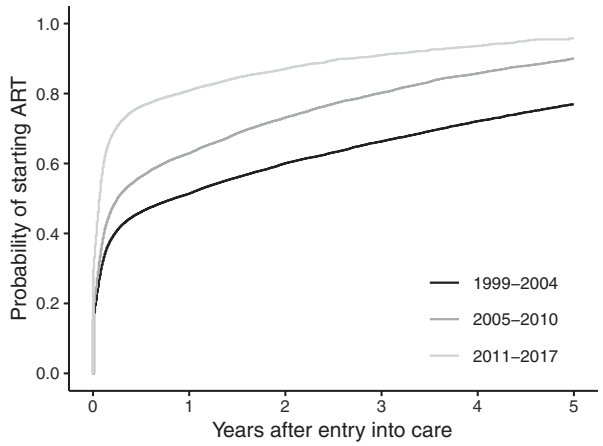

Figure 1. Probability of starting antiretroviral (ART) over time since entry into human immunodeficiency virus (HIV) care by calendar period among 82 766 patients entering care at US North American AIDS Cohort Collaboration clinical sites between 1999 and 2017.

modest because many patients in the observed NA-ACCORD data did, in fact, receive HIV treatment soon after entry into care. In addition, over the course of the study, treatment guidelines evolved to recommend earlier treatment and the time from entry into care until treatment initiation declined [5]. Therefore, the number of patients whose treatment patterns would have been altered by this intervention declined over time. We would expect to see a stronger effect in a setting (or subgroup) with longer delays in access to treatment or under an intervention to ensure treatment within a smaller time window (eg, within 24 hours, 72 hours, or 1 week of entering care) [35–37].

The remaining elevation in mortality rate observed under universal early treatment initiation could have several causes. Even highly effective treatments may be imperfect, and with increasing life expectancy among people with HIV, the long-term effects of both HIV and ART are only beginning to be more fully observed [17].

Most importantly, early treatment after entry to HIV care is not the same as early treatment for HIV infection because people entering HIV care may have lived for years with uncontrolled HIV before diagnosis and linkage to care. In the current study, the median CD4 cell count at study entry remained low (366/μL; <200/μL in nearly 20%) even in the most recent time period, and other studies in NA-ACCORD and elsewhere have noted that CD4 cell count at entry into care and treatment initiation remains below 400/μL [5, 38, 39]. With an average CD4 cell count decline of approximately 60 cells/μL per year [40], a majority of people entering care at an NA-ACCORD site in our cohort were likely untreated for ≥5 years before entry. Until this infection-to-treatment gap is closed, mortality risks are unlikely to approach those of people without HIV.

The elevation in 5-year mortality observed among people with HIV may also be due in part to their higher risk of other chronic conditions, including metabolic and mental health disorders, and higher prevalence of smoking and substance abuse [14–16, 41–47]. While many of these factors likely manifested before HIV diagnosis, routine engagement with HIV care may offer opportunities to address these factors by providing a forum for early diagnosis, referrals for care, and connection with appropriate resources.

Our results should be interpreted considering the study's limitations. We matched on measured demographic and

Table 2. Five-Year Mortality Risks, Mortality Risk Differences, and Mortality Risk Ratios in 82 766 Patients Entering Care for Human Immunodeficiency Virus in 1999–2017, Under Observed Treatment Patterns and Presumption of Early Treatment, and in a Matched Subset of the General US Population, Overall and by Calendar Period

Patient Group or Population	5-y Mortality Risk, %	Mortality Risk Difference (95% CI), %	Mortality Risk Ratio (95% CI)
Patients entering HIV care during all periods (1999–2017)			
Under observed treatment patterns	10.9	7.9 (7.6–8.2)	3.68 (3.57–3.79)
Under universal early treatment[a]	10.1	7.2 (5.8–8.6)	3.44 (3.29–3.59)
Matched general US population	2.9	0	1
Patients entering HIV care in 1999–2004			
Under observed treatment patterns	15.1	11.7 (11.1–12.2)	4.43 (4.27–4.54)
Under universal early treatment[a]	14.1	10.7 (8.7–12.6)	4.13 (3.92–4.37)
Matched general US population	3.4	0	1
Patients entering HIV care in 2005–2010			
Under observed treatment patterns	8.7	5.7 (5.3–6.2)	2.94 (2.79–3.09)
Under universal early treatment[a]	8.4	5.4 (3.6–7.3)	2.84 (2.64–3.05)
Matched general US population	2.9	0	1
Patients entering HIV care in 2011–2017			
Under observed treatment patterns	4.9	2.6 (2.0–3.3)	2.12 (1.86–2.42)
Under universal early treatment[a]	4.4	2.1 (−0.0 to 4.2)	1.8 (1.52–2.35)
Matched general US population	2.3	0	1

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

[a]Treatment within 3 months of entry into care.

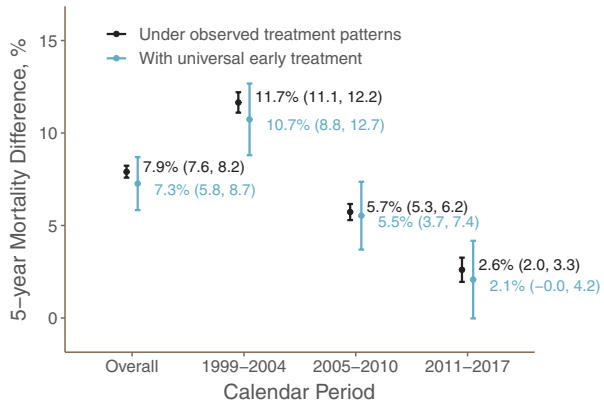

Figure 2. Five-year mortality differences (with 95% confidence intervals [CIs]) comparing mortality risks between the matched US general population and 82 766 patients entering care for human immunodeficiency virus at US North American AIDS Cohort Collaboration clinical sites between 1999 and 2017 under both observed treatment patterns (*black*) and universal early treatment (*blue*). Points represent mortality risk differences, and lines, 95% CIs.

geographic factors thought to be associated with both HIV and mortality to account for differences between those with HIV and the general population. However, some factors were unmeasured and therefore not accounted for in this analysis. For example, both NA-ACCORD and NCHS lacked information on socioeconomic status and neighborhood, which are related to both HIV incidence and mortality [13, 48–50]. Other factors may have been measured imperfectly. For example, we matched people entering HIV care to people in the US population based on zip code at entry into care; some of these individuals may have moved during the 5-year follow-up and those with 3-digit zip codes matched to more than 1 county.

Moreover, our estimates of risk under early treatment may have been subject to bias if there were unmeasured covariates that were associated with both treatment timing and mortality. For example, if current injection drug use and housing instability, both unmeasured, were associated with later treatment and higher mortality risks, early treatment may have appeared misleadingly effective. While we included the set of covariates typically used to model the effects of ART [51, 52] and treatment timing [53], these social determinants of health (and others, like education and income) may be responsible in part for both the gap in mortality risks between those with HIV and the US population and between those with HIV with or without early treatment.

HIV clinical care has made immense gains in improving survival for people with HIV, but we estimate that they would continue to have higher 5-year mortality risks than the US population even if started on ART within 3 months of entry into care. Further reducing this remaining elevation in mortality risks will likely require reducing the time from HIV infection to linkage to care [54–57] and may require additional strategies aimed at treating and preventing other chronic conditions among people receiving HIV care.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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