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Association of Incomplete Adherence to Antiretroviral Therapy With Cardiovascular Events and Mortality in Virologically Suppressed Persons With HIV: The Swiss HIV Cohort Study

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Background. Incomplete antiretroviral therapy (ART) adherence, even if sufficient to maintain viral suppression, is associated with enhanced inflammation in persons with HIV (PWH). However, its clinical implications remain unknown.

Methods. PWH enrolled in the Swiss HIV Cohort Study without a history of cardiovascular disease (CVD) who initiated ART between 2003 and 2018 and had viral suppression (<50 copies/mL) for ≥6 months were evaluated. The association between incomplete self-reported ART adherence (≥1 or ≥2 missed doses in the last month) and (1) any CVD event (myocardial infarction, revascularization, cerebral hemorrhage, stroke, and/or death due to CVD event) or (2) non-CVD-related death was evaluated using adjusted Cox proportional hazards models.

Results. A total of 6971 PWH (74% male) were included in the analysis (median age [interquartile range {IQR}], 39 [32–47] years). The median (IQR) follow-up was 8 (4–11) years, with 14 (8–23) adherence questionnaires collected per participant. In total, 205 (3%) participants experienced a CVD event, and 186 (3%) died a non-CVD-related death. In an adjusted competing risk model where missing data were imputed, missing ≥1 ART dose showed an increased, but not statistically significant, risk for CVD events (hazard ratio [HR], 1.23; 95% CI, 0.85–1.79; $P = .28$). Non-CVD-related mortality showed a statistically significantly increased risk with missing ≥1 ART dose (HR, 1.44; 95% CI, 1.00–2.07; $P = .05$) and missing ≥2 ART doses (HR, 2.21; 95% CI, 1.37–3.57; $P = .001$).

Conclusions. Incomplete ART adherence was significantly associated with an increased risk for non-CVD-related mortality in PWH with virologic suppression. This highlights the potential role of nonadherence to ART as a driver of non-AIDS clinical outcomes.

Keywords. adherence; antiretroviral therapy; cardiovascular disease; viral suppression.

Despite achieving suppressed viral replication by conventional assays, persons with HIV (PWH) taking antiretroviral therapy (ART) have residual systemic inflammation that has been associated with the development of serious non-AIDS events and increased all-cause mortality [1, 2]. While the underlying causes of this residual inflammation and immune activation are not completely understood, they are likely to be multifactorial, requiring a multitargeted approach to reduce the inflammation [3]. Recently, ART nonadherence has been evaluated as a potential driver of the chronic inflammation observed in this population. Recent data have demonstrated that incomplete ART adherence is associated with increased levels of systemic inflammation, immune activation, and coagulopathy in virologically suppressed individuals [4–8] and that optimal adherence may lead to levels of inflammation similar to those observed in persons without HIV [9]. Several potential mechanisms to explain this association have been proposed, in particular that incomplete adherence could result in intermittent low-level HIV replication (ie, below the limit of detection by clinically available assays) [10–12], resulting in enhanced inflammation and immune activation [13, 14]. However, despite being identified in several studies, the association of incomplete adherence with

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chronic residual inflammation in PWH who are virally suppressed currently lacks clinical significance.

Several—but not all—studies have demonstrated that, compared with persons without HIV, PWH may be at increased risk of developing cardiovascular disease (CVD) [3, 15–21]. In particular, PWH have an increased risk of myocardial infarction (MI), which has been postulated to be driven by traditional cardiovascular risk factors, but also by HIV-specific risk factors such as type of ART, CD4+ T-cell count, and HIV viremia [16, 22]. Chronic residual inflammation has also been postulated as a major contributor to the increased cardiovascular risk in PWH by promoting atherosclerosis [23–27]. Given its association with residual inflammation, immune activation, and coagulopathy, incomplete ART adherence could also lead to an increased frequency of atherosclerotic CVD, even in the setting of viral suppression, which was the focus of this study.

METHODS

Study Cohort and Participants

The SHCS is a prospective multicenter study cohort that follows ~75% of all PWH on ART in Switzerland [28] and has enrolled participants since 1988 from within 7 outpatient HIV clinics at participating medical centers (Basel, Bern, Geneva, Lausanne, Lugano, St. Gallen, and Zurich) or from private physicians [29]. Study visits in the SHCS occur every 6 months and include review of medical history and new diagnoses, physical examinations, medication review, evaluation of ART adherence, and laboratory evaluations, as previously described [30].

We conducted an analysis of PWH registered in the SHCS and initiating ART between January 1, 2003 (introduction of ART adherence questionnaire), and December 31, 2018. Participants were required to have ≥6 months of viral suppression (HIV-1 RNA < 50 copies/mL) and no history of CVD at baseline. Viral blips (HIV-1 RNA ≥50 copies/mL and <400 copies/mL followed by an HIV-1 RNA VL <50 copies/mL) were allowed and included as time-dependent variables. Database closure was on January 31, 2020.

Outcomes

Participants were determined to have a CVD event if they developed any of the following clinical entities from within a composite outcome, as previously described [31–34]: myocardial infarction (MI), revascularization (coronary angioplasty/stenting, coronary artery by-pass grafting, carotid endarterectomy, procedures on other arteries), cerebral hemorrhage, cerebral infarction (stroke), and/or death due to cardiovascular disease. Framingham risk score (FRS) was calculated using a validated formula, as previously described [35].

ART Adherence

Adherence in the SHCS is assessed using a simplified and validated self-reported questionnaire that contains 2 questions (asked by the participant's clinician), as previously described [36–38]. "Adherence" is assessed by the question "How often did you miss a dose in the last 4 weeks?" (daily, more than once a week, once a week, once every second week, once a month, never). "Drug holidays" are assessed by the question "Did you have a period of no drug intake for >24 hours in the last 4 weeks?" (yes/no) [38]. Two definitions of incomplete ART adherence were utilized, (a) ≥1 and (b) ≥2 missed ART doses in the last 4 weeks, to reflect any missed doses in the last 4 weeks. These definitions have previously been associated with viral failure [37, 39], mortality [39], and drug resistance [40] in this cohort. We selected a relatively high adherence threshold (ie, any missed doses) based on our previous research, where <100% adherence has been associated with heightened residual inflammation, immune activation, and coagulopathy [4–7].

Statistical Analysis

Baseline was defined as the date the participant suppressed their viral load for 24 weeks. Descriptive statistics were used to summarize baseline characteristics and outcomes. We estimated cause-specific event rates for CVD, mortality, and viral failure using cumulative incidences [41, 42] and assessed factors associated with cause-specific events using various Cox proportional hazard ratio (HR) models [41]. In addition to a univariate model that evaluated the association of incomplete adherence with CVD events, we evaluated additional models that assessed for competing risk from non-CVD-related death. This was intended to account for the possibility that a participant could have experienced this event, which might compete with the outcome of interest, thus hindering the observation or the chance that the event of interest occurred. Time at risk excluded periods when participants were lost to follow-up/transferred to other clinics, at which point participants were censored.

To address missing baseline covariates, we used multiple imputation with chained equations, assuming data were missing at random [43]. In the imputations, we used multinomial regression for FRS category; truncated regression for inverse-square-root-transformed BMI, square-root-transformed cholesterol, HDL, systolic blood pressure, square-root-transformed CD4+ T-cell count, and square-root-transformed log of HIV-1 RNA; and logistic regression for injecting drug use, smoking, Caucasian ethnicity, and family history of CVD (ie, history of MI or stroke before age 50 in any first-degree relatives). In addition to the baseline covariates, we included adherence across all follow-up in the imputations, an indicator for outcome (CVD, death due to non-CVD-related or unknown causes, or censored), and the Nelson-Aalen estimator of the baseline cumulative hazard [43, 44]. We used 10 imputations, based on at least the approximate fraction of missing information [45]. All analyses were conducted in Stata, version 15 (StatCorp LLC).

Patient Consent Statement

All patients who are part of the SHCS have given their written consent to use their data for research purposes.

RESULTS

Study Population

A total of 7883 PWH initiated ART between 2003 and 2018. Of these, 912 (12%) were excluded for the following reasons: 450 were not on ART for at least 12 months, 8 had no VL done after starting ART, 288 did not achieve viral suppression (n = 58) or were not suppressed for a minimum of 24 weeks (n = 230), 120 had a CVD event before baseline, and 46 did not have adherence information recorded during follow-up. Table 1 shows the demographic characteristics of the 6971 PWH included in the study population according to outcome. Overall, the median (interquartile range [IQR]) age was 39 (32–47) years; 5164 (74%) of the cohort were male and 5084 (73%) were Caucasian. A total of 709 (11%) participants had a family history of CVD, 2252 (37%) were overweight or obese, and 2493 (41%) were smokers. Diabetes was present in 150 (2%) participants, and 450 (8%) had an FRS >20%.

ART Adherence and Clinical Outcomes

In multivariable models, missing ≥1 ART dose in the past 4 weeks as assessed by a questionnaire was associated with an HR of 1.11 (95% CI, 0.76–1.61; $P = .59$) for CVD events in univariate analysis and 1.35 (95% CI, 0.90–2.03; $P = .15$) in multivariate analysis (Table 2, Model 1a). When missing data were imputed, the multivariate HR was 1.23 (95% CI, 0.85–1.79; $P = .28$) (Table 2, Model 2a). Finally, our findings for the HR for CVD events and non-CVD-related death were comparable when missing ≥2 ART doses was evaluated as the predictor (Table 2, Models 1b and 2b).

For the outcome of non-CVD-related mortality, we found that missing ≥1 dose of ART was associated with an HR for non-CVD-related mortality of 1.46 (95% CI, 1.02–2.09; $P = .04$) in univariate analyses and 1.44 (95% CI, 1.00–2.07; $P = .05$) in multivariate analyses where missing data were imputed, respectively (Table 2, Model 2a). In a model that assessed ≥2 missed ART doses, the HR was 2.21 (95% CI, 1.38–3.56; $P = .001$) in a univariate model and 2.21 (95% CI, 1.37–3.57; $P = .001$) in a multivariate model when missing data were imputed (Table 2, Model 2b).

In a sensitivity analysis that excluded the presence of viral blips from the model, the results remained almost identical to our original findings.

Factors Associated With CVD Events and Non-CVD-Related Mortality

The participant demographic and clinical factors associated with our outcome(s) of interest in Model 2b are presented in Supplementary Table 1. In addition to missing ≥2 doses of ART, Caucasian ethnicity, being underweight, having a positive family history of CVD disease, intravenous drug use as an HIV risk factor, and having an FRS >10% were all associated with a higher risk of CVD events or non-CVD-related death. Comparatively, being overweight, having a CD4 T-cell count between 350 and 499 cells/mm^3, and having an HIV-1 RNA between 10 000 and 49 999 at the time of ART initiation were associated with a lower risk of non-CVD-related death.

DISCUSSION

In this study, we aimed to evaluate the association between incomplete ART adherence and CVD events in a large observational cohort of PWH who were virologically suppressed to <50 copies/mL. Although not significant, we identified a positive association between these 2 variables, with a direction and magnitude that were consistent when we evaluated several models that considered non-CVD-related death as a competing risk and after imputing missing data. While not the initial goal of our study, we identified a significant association between incomplete ART adherence and an increased hazard of non-CVD-related death in the study population. This association, which remained significant both in univariate and multivariate analyses and after imputing missing data, is of unique clinical importance because it identifies adherence to ART as a potentially actionable risk factor that could be targeted to reduce mortality in PWH who maintain viral suppression. While previous studies have repeatedly demonstrated an association of incomplete adherence with high residual inflammation in virally suppressed PWH [4–7], this is the first study, to our knowledge, to identify a non-AIDS adverse clinical outcome (non-CVD-related death and CVD event) associated with incomplete (but suppressive) adherence to ART.

As has been previously proposed [4, 6, 7, 46], several potential mechanisms could explain our findings. These include intermittent viral replication below the limit of detection in plasma [10, 12] or tissue (ie, lymphoid and/or gut tissue) [47] where drug penetration is suboptimal [48], resulting in enhanced residual inflammation exacerbated by incomplete adherence. However, the clinical consequences of this residual viral replication remain controversial. While a recent AIDS Clinical Trials Group study (A5321) did not find a correlation between residual viral replication (using single-copy assays) and residual inflammation, this analysis focused on a highly selected cohort of participants who had long-standing viral suppression (median, 7 years) and were originally enrolled in clinical trials [49]. In comparison, other studies in different cohorts have identified associations of residual viremia and HIV-DNA with inflammation [14, 50, 51] and with increased cardiovascular morbidity [26, 27]. Given the well-established association between residual inflammation and morbidity/mortality in HIV [24, 25], it remains plausible that suboptimal ART adherence could trigger episodes of residual HIV replication and heightened inflammation that result

Table 1. Baseline Characteristics by Study Outcome

Characteristic	CVD-Related Event (n = 205)	Non-CVD-Related Death (n = 186)	Censored (n = 6850)	Total (n = 6971)
Age, median (IQR), y	49 (43–56)	46 (40–55)	39 (32–46)	39 (32–47)
Missing	0	0	0	0
Gender				
Male	172 (84)	137 (74)	4855 (74)	5164 (74)
Female	33 (16)	49 (26)	1725 (26)	1807 (26)
Missing	0	0	0	0
Caucasian				
No	16 (8)	23 (12)	1842 (28)	1881 (27)
Yes	189 (92)	163 (88)	4732 (72)	5084 (73)
Missing	0	0	6	6
Basic education (9 y)				
No	171 (83)	137 (74)	5041 (77)	5349 (77)
Yes	34 (17)	48 (26)	1502 (23)	1584 (23)
Missing	0	1	37	38
HIV transmission risk				
Homosexual	95 (47)	63 (36)	3301 (52)	3459 (52)
Heterosexual	82 (41)	65 (37)	2514 (40)	2661 (40)
Injecting drug use	22 (11)	45 (25)	403 (6)	470 (7)
Other	2 (1)	4 (2)	104 (2)	110 (2)
Missing	4	9	258	271
Body mass index category				
Underweight	7 (4)	14 (8)	185 (3)	206 (3)
Normal weight	110 (59)	109 (64)	3338 (59)	3557 (59)
Overweight	56 (30)	35 (20)	1653 (29)	1744 (29)
Obese	14 (7)	13 (8)	481 (9)	508 (8)
Missing	18	15	923	956
Family history of CV disease				
No	166 (83)	154 (85)	5632 (90)	5952 (89)
Yes	34 (17)	28 (15)	647 (10)	709 (11)
Missing	5	4	301	310
Smoker				
No	88 (46)	60 (35)	3416 (60)	3564 (59)
Yes	103 (54)	113 (65)	2277 (40)	2493 (41)
Missing	14	13	887	914
Systolic blood pressure, median (IQR)	128 (120–140)	126 (115–137)	124 (115–134)	124 (115–135)
Missing	19	11	933	963
Diabetes				
No	193 (94)	176 (95)	6452 (98)	6821 (98)
Yes	12 (6)	10 (5)	128 (2)	150 (2)
Missing	0	0	0	0
On hypertensive treatment				
No	189 (92)	162 (87)	6306 (96)	6657 (95)
Yes	16 (8)	24 (13)	274 (4)	314 (5)
Missing	0	0	0	0
Total cholesterol, median (IQR), mg/dL	204 (174–236)	182 (148–210)	183 (159–213)	184 (159–213)
Missing	15	7	769	791
HDL cholesterol, median (IQR), mg/dL	44 (36–54)	50 (39–62)	46 (39–57)	46 (39–57)
Missing	16	7	782	805
Framingham risk score				
<10%	66 (36)	97 (56)	4377 (78)	4540 (76)
10%–20%	63 (34)	47 (27)	841 (15)	951 (16)
>20%	54 (30)	28 (16)	368 (7)	450 (8)
Missing	22	14	994	1030
ART regimen at ART initiation				
Non-nucleoside reverse transcriptase inhibitors	92 (45)	65 (35)	2531 (38)	2688 (39)
Protease inhibitors	101 (49)	104 (56)	2745 (42)	2950 (42)

Table 1. Continued

Characteristic	CVD-Related Event (n = 205)	Non-CVD-Related Death (n = 186)	Censored (n = 6850)	Total (n = 6971)
Integrase inhibitors	8 (4)	10 (5)	1123 (17)	1141 (16)
Other	4 (2)	7 (4)	181 (3)	192 (3)
Missing	0	0	0	0
CD4+ T-cell count at ART initiation, median (IQR), cells/mm^3	235 (140–358)	215 (112–320)	285 (170–418)	280 (167–414)
0–199	75 (40)	79 (46)	1730 (31)	1884 (31)
200–349	63 (33)	58 (34)	1903 (34)	2024 (34)
350–499	30 (16)	18 (11)	1124 (20)	1172 (19)
≥500	21 (11)	16 (9)	899 (16)	936 (16)
Missing	16	15	924	955
HIV-1 RNA at ART initiation, median (IQR), copies/mL	11 (9–12)	11 (8–12)	11 (9–12)	11 (9–12)
0–9999	56 (30)	61 (36)	1624 (29)	1741 (29)
10 000–49 999	36 (19)	20 (12)	1409 (25)	1465 (25)
≥50 000	97 (51)	88 (52)	2570 (46)	2755 (46)
Missing	16	17	977	1010

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; CV, cardiovascular; CVD, cardiovascular disease; HDL, high-density lipoprotein; IQR, interquartile range.

in adverse non-AIDS clinical outcomes despite virologic suppression in plasma.

Another explanatory mechanism behind our findings could be that incomplete adherence identifies a subset of patients who develop intermittent viremia that is not captured between clinic visits [4], in particular given the antiviral potency and pharmacokinetic forgiveness of the new antiretrovirals and the current trends toward less frequent monitoring in clinical care [52, 53]. This was particularly highlighted by the stronger association observed in PWH who missed ≥2 ART doses, suggesting that the clinical consequences of incomplete ART adherence could be accentuated in a subgroup of patients with sustained low adherence. Whether incomplete ART adherence leads to intermittent viremia has also been a matter of constant debate, as some studies have shown a clear association between them [10, 11], while others have refuted this theory [54]. However, the potential association between lapses in ART adherence and adverse clinical outcomes could help reframe the conversation between clinicians and patients about the importance of aiming toward the highest possible adherence.

A third potential mechanism to explain our findings is that incomplete ART adherence could be a surrogate for low adherence to other medications such as antihypertensives, statins, and/or antidiabetics, which was not assessed in our study, or that incomplete ART adherence could be associated with unmeasured bias inherent to a cohort study. This potential explanation is clinically relevant, as it could lead to a discussion about adherence to non-ART medications, which has been suggested to be lower when compared with ART in some studies [55]. While most of the focus on achieving and sustaining viral suppression in clinical practice is currently aimed at preventing progression to AIDS and/or transmission to others, the potential deleterious consequences of incomplete ART adherence (despite suppression) might become more relevant in the coming years, in particular given the accumulation of clinical comorbidities in an aging population of PWH.

As expected, risk factors that have been previously well established to be associated with CVD events, such as Caucasian ethnicity, family history of CVD disease and a high FRS, were also observed in our group of PWH with virologic suppression [35]. This highlights the importance of identifying modifiable CVD risk factors in clinical care and prevention of PWH on suppressive ART. It also underscores the possibility that ART adherence may have considerable clinical relevance beyond virologic suppression. In particular, our identified association raises the question of whether improving ART adherence may be a modifiable target to reduce residual inflammation and immune activation [6] and prevent CVD outcomes and mortality. Indirect evidence of this has been recently observed in a subanalysis performed by the Multicenter AIDS Cohort Study (MACS), where men with HIV who were virologically suppressed (<50 copies/mL) and who reported 100% ART adherence had similar concentrations of interleukin-6 (IL-6), soluble interleukin-6 receptor (sIL-6R), IL-1β, and interferon-γ, among other biomarkers, when compared with men without HIV, suggesting that sustained and high ART adherence could lead to normalization of these biomarkers [9] and translate into clinical benefit. This hypothesis is especially supported by the normalization of IL-6 given the strong association of this inflammatory cytokine with CVD events and mortality in PWH [24, 56]. As we have limited effective strategies to reduce inflammation in treated HIV disease, future studies that evaluate whether an intervention aimed at improving ART adherence beyond suppression could reduce residual inflammation and prevent CVD outcomes and non-CVD-related death are required.

Our study has several strengths. First, we evaluated a very large and well-characterized clinical "real-world" cohort rather

Table 2. Independent Association Between Incomplete ART Adherence With CVD Events and Non-CVD-Related Mortality in Virally Suppressed Study Participants on ART

Characteristic	CVD-Related Events[a] Univariate/Multivariate	*P* Value	Non-CVD-Related Mortality[b] Univariate/Multivariate	*P* Value
Incomplete ART adherence[c] Missed ≥1 dose of ART in the last 4 wk				
Model 1a: only considering CVD-related events	205/163			
Univariate, n = 6971	1.11 (0.76–1.61)	0.59		
Multivariate, n = 4750	1.35 (0.90–2.03)	0.15		
Model 2a: Competing risk models with non-CVD-related death as a competing event with missing data imputed	205/205		186/186	
Univariate, n = 6971	1.11 (0.76–1.61)	0.59	1.46 (1.02–2.09)	.04
Multivariate, n = 6971	1.23 (0.85–1.79)	0.28	1.44 (1.00–2.07)	.05
Incomplete ART adherence[c] Missed ≥2 doses of ART in the last 4 wk				
Model 1b: only considering CVD-related events	205/163			
Univariate, n = 6971	1.08 (0.59–1.99)	0.80		
Multivariate, n = 4750	1.32 (0.67–2.61)	0.42		
Model 2b: Competing risk models with non-CVD-related death as a competing event with missing data imputed	205/205		186/186	
Univariate, n = 6971	1.08 (0.59–1.99)	0.78	2.21 (1.38–3.56)	.001
Multivariate, n = 6971	1.25 (0.68–2.31)	0.48	2.21 (1.37–3.57)	.001

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CVD, cardiovascular disease; HR, hazard ratio.

[a]CVD events include myocardial infarction, revascularization, cerebral hemorrhage, stroke, and/or death due to cardiovascular event.

[b]All reported deaths except those determined to be due to CVD.

[c]Results give the HR and 95% CI; competing risk models give the cause-specific HR; adjusted models include gender, Caucasian ethnicity, injecting drug use, BMI, family history of CVD, Framingham risk score category, $CD4^+$ T-cell count at ART initiation, HIV-1 RNA at ART initiation, first ART regimen class, and HIV-1 viral blips (single HIV-1 RNA >400 copies/mL followed by HIV-1 RNA <50 copies/mL).

than a clinical trial cohort, which provides generalizability to our findings. However, our cohort was not racially diverse, as only 26% of our population was non-Caucasian, which could limit the interpretation of our findings to resource-limited settings where HIV is highly prevalent. Second, compared with previous studies evaluating ART adherence and inflammation [4–6], our study encompassed a long follow-up period (2003–2020) that included both the pre– and post–integrase inhibitor eras. Third, adjudication of CVD (and other) events in the SHCS occurs centrally within the Data collection on Adverse events of Anti-HIV Drugs (D:A:D) study, which supports consistency in our study outcomes [57]. Lastly, although the association of incomplete ART adherence with CVD events was not significant, the direction and consistency of our results across models that considered both competing events and multiple imputation for missing data support the strength of our conclusions. The lack of statistical significance was likely due to the relatively low frequency of events observed in our cohort in the observed study period. Thus, future studies utilizing more sensitive adherence measures (eg, objective or pharmacologic measures) where a larger number of CVD events are observed could lead to stronger and more significant associations. Among the weaknesses of our study were that non-CVD-related death is a heterogeneous category that will need to be refined in future studies assessing the association between ART adherence and mortality and that we only focused on atherosclerotic CVD (ie, we excluded heart failure). Furthermore, we evaluated ART adherence based on self-report, which can overestimate adherence [53]. This could have resulted in misclassification of some participants as adherent when they really were not and in an attenuation of the observed associations. Future studies utilizing objective pharmacologic measures—such as real-time monitoring or pharmacologic measures in diverse clinical cohorts—are needed.

In conclusion, our study demonstrated that incomplete (ie, <100%) ART adherence is associated with an increased risk for non-CVD-related mortality in PWH who are virologically suppressed to <50 copies/mL. These findings suggest the potential critical role that ART adherence could have in improving clinical outcomes and open the door for further research on the role that increasing adherence—beyond suppression—could have in preventing morbidity/mortality in PWH who are considered optimally treated. Future studies to confirm this association and to understand its clinical implications are needed.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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