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Review

Clinical events associated with poor CD4$^+$ T-cell recovery in people living with HIV following ART: A systematic review and meta-analysis

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SUMMARY

Background: Antiretroviral therapy (ART) has significantly improved outcomes for people living with HIV (PLWH), but poor CD4$^+$ T-cell recovery remains a challenge. This study aimed to evaluate the relationship between poor CD4$^+$ T-cell recovery and the morbidity of clinical events (CEs) in PLWH after ART initiation.

Methods: We conducted a comprehensive search of the EMBASE, PubMed, Web of Science, and Cochrane Library databases up to February 19, 2024, and included studies that reported the number of CEs along with the CD4 count at the time of the CEs or the most recent CD4 count prior to the CEs. A random-effects model was employed for meta-analysis to calculate odds ratios (ORs) and their 95% confidence intervals (CIs) for CEs at different CD4 count thresholds.

Findings: We included 15 studies with 54,766 PLWH and reported a significant inverse correlation between CD4$^+$ T-cell counts and the morbidity of both AIDS-defining events (ADEs) and non-AIDS-defining infections (NADIs). However, CD4$^+$ T-cell counts were not significantly associated with non-AIDS-defining noninfections (NADNIs). Compared with individuals with normal CD4 counts (> 500 cells/μL), those with CD4 counts < 200 cells/μL and 200–350 cells/μL exhibited higher ADEs morbidity, with ORs of 7·04 (95% CI: 1·77–28·03) and 1·63 (95% CI: 1·36–1·97), respectively. Similarly, individuals with CD4 counts < 200 cells/μL showed a higher morbidity of NADIs (OR = 2·82, 95% CI: 1·50–5·31). However, no significant difference in NADNI morbidity was observed between groups with poor CD4$^+$ T-cell recovery and those with normal CD4 counts.

Interpretation: This meta-analysis revealed an inverse relationship between CD4$^+$ T-cell counts and morbidity associated with ADEs and NADIs in PLWH after ART initiation, with key thresholds of 350 cells/μL and 200 cells/μL. No significant associations were found between CD4 counts and NADNIs. These results highlight the need for comprehensive patient care that goes beyond monitoring only CD4 counts.

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Research in Context

Evidence before this study

HIV infection management remains a critical global public health challenge. To elucidate the relationship between $CD4^+$ T-cell counts and clinical outcomes in people living with HIV (PLWH), we conducted a comprehensive systematic search of the EMBASE, PubMed, Web-of-Science, and Cochrane Library databases for relevant studies published up to February 19, 2024. Our search strategy employed key terms including "HIV", "CD4", "antiretroviral therapy", "AIDS-defining events", "non-AIDS-defining events", and their variants. The literature review revealed a substantial body of individual studies examining the associations between $CD4^+$ T-cell counts and clinical outcomes in PLWH undergoing antiretroviral therapy (ART). These investigations consistently demonstrated an inverse relationship between CD4 counts and the risk of AIDS-defining events (ADEs) and non-AIDS-defining events (NADEs). However, our literature review revealed that a comprehensive meta-analysis synthesizing this evidence is currently lacking.

Added value of this study

Our meta-analysis offers novel, quantitative insights into the complex relationship between CD4 counts and clinical events in PLWH. We established a significant inverse correlation between CD4 counts and the morbidity rates of both ADEs and non-AIDS-defining infections (NADIs). Notably, our findings delineate critical CD4 count thresholds: the morbidity rate of ADEs increases markedly below 350 cells/μL, whereas the morbidity rate of NADIs increases significantly when CD4 counts fall below 200 cells/μL. Intriguingly, we observed no significant association between CD4 counts and the morbidity of non-AIDS-defining noninfections (NADNIs).

Implications of all the available evidence

The findings of our meta-analysis have far-reaching implications for both clinical practice and public health strategies in HIV management. First, they emphasize the critical importance of maintaining CD4 counts above specific thresholds to mitigate the risk of ADEs and NADIs in PLWH. This understanding can assist clinicians in making more informed decisions regarding treatment intensification or modification for patients with inadequate $CD4^+$ T-cell recovery. Second, our findings suggest that more frequent monitoring appears beneficial for patients with CD4 counts below 200 cells/μL, whereas monitoring schedule monitoring could be optional in those with counts above 350 cells/μL. Furthermore, the lack of association between CD4 counts and NADNIs highlights the need for comprehensive care that addresses other risk factors beyond immunological recovery.

Introduction

Since its introduction, antiretroviral therapy (ART) has revolutionized the treatment landscape for people living with HIV (PLWH), becoming the cornerstone of HIV management.[1] ART effectively suppresses HIV viral replication, leading to significant improvements in immune function and a marked reduction in AIDS-related morbidity.[2] However, despite the generally positive outcomes associated with ART, a subset of patients experience suboptimal immune reconstitution, a phenomenon known as poor $CD4^+$ T-cell recovery.[3]

Poor $CD4^+$ T-cell recovery, characterized by the failure of the $CD4^+$ T-cell count to reach the expected level (typically > 500 cells/μL) despite effective viral suppression, remains a significant challenge in HIV care. This phenomenon is influenced by various factors, including the baseline CD4 cell count, timing of ART initiation, presence of coinfections, and individual immune responses.[3,4] Persistently low CD4 counts despite ART-mediated viral suppression are associated with an increased risk of clinical events (CEs) and mortality.[5]

CEs in PLWH can be broadly categorized into AIDS-defining events (ADEs) and non-AIDS-defining events (NADEs).[6] ADEs primarily encompass opportunistic infections and AIDS-defining cancers, while NADEs are further subdivided into non-AIDS-defining infections (NADIs) and non-AIDS-defining noninfections (NADNIs).[7] Previous studies revealed an inverse correlation between CD4 counts and the risk of ADEs, with the CD4 count emerging as an independent predictor of ADE risk, surpassing even the prognostic value of the viral load.[8,9] Similarly, during periods of viral suppression mediated by ART, lower CD4 counts are significantly associated with an increased risk of NADEs.[10] This association extends beyond NADIs to encompass various NADNIs, including stroke, cardiovascular disease, liver disease, and non-AIDS-defining cancers.[11,12]

On the basis of the understanding of the relationship between CD4 counts and CEs, a guideline issued by the U.S. Department of Health and Human Services (HHS) has been formulated to adjust the CD4 count monitoring frequency.[3] Specifically, during the first two years of ART initiation (assuming effective viral suppression), patients with CD4 counts below 300 cells/μL are advised to undergo testing every three months, while those with CD4 counts at or above 300 cells/μL may extend their testing intervals to every six months. However, despite the availability of guidelines and numerous clinical studies, there remains a lack of comprehensive meta-analysis systematically evaluating the relationship between poor $CD4^+$ T-cell recovery and the morbidity of various CEs in PLWH undergoing ART. This gap in evidence-based medicine hinders the optimization of monitoring strategies and patient care.

This meta-analysis aims to evaluate the morbidity rate of CEs in PLWH who exhibit poor $CD4^+$ T-cell recovery following ART. By synthesizing existing evidence, our study provides insights into the implications of poor immune reconstitution, potentially refining CD4 count monitoring strategies and improving clinical outcomes for PLWH.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines.[13] Our protocol was prospectively registered with PROSPERO (CRD42023477945). We performed a comprehensive search of four electronic databases (EMBASE, PubMed, Web-of-Science and the Cochrane Library) to identify studies reporting the associations between CD4 counts and both ADEs and NADEs following ART initiation. The search strategy employed the following key terms: "HIV", "CD4", "antiretroviral therapy", "AIDS-defining events", "non-AIDS-defining events", and their variants (see appendix table S1 for the complete search strategy). No restrictions were imposed on language, publication date, document type, or publication status for study inclusion. The literature search was conducted on February 19, 2024.

We first screened articles by title and abstract, and then screened the full texts for eligible studies. We included the following observational studies: (1) those involving PLWH who received ART, irrespective of the effectiveness of viral suppression; (2) studies

reporting the number of CEs; and (3) studies reporting the CD4 count at the time of CE occurrence or the most recent CD4 count prior to the event.

We excluded studies that: (1) involved PLWH who had comorbidities (e.g., tuberculosis or hepatitis coinfection); (2) did not specify the timing of CD4 count measurement or where the measurement was not taken at the time of or shortly before the occurrence of CEs; (3) had data overlapping with other studies; (4) had a follow-up time of less than 2 years; and (5) were abstracts, letters, case reports, or reviews. Additionally, we excluded studies conducted prior to 1995, as they were conducted during the pre-ART era, a time when treatment strategies differed significantly from those in the ART era. Two investigators (TM and KCG) independently screened the titles and abstracts, and discrepancies were resolved by a third investigator (GZ).

Data analysis

Non-English/foreign-language abstracts and articles were accurately translated for full-text review. In a preconceived and standardized data extraction form, information was collected on the first author's name, year of publication, title, journal, study country, study design, patient demographics, duration of ART, total number of cases assessed, CD4 count, total number of participants in each subgroup of CD4, and number of CEs, ADEs, NADEs, NADIs, and NADNIs per subgroup for CD4. Two investigators (TM and KCG) independently conducted the data extraction, cross-checked the extracted data, and discrepancies were resolved by a third investigator (GZ).

We used the Newcastle Ottawa Scale (NOS), with reference to previous meta-analyses, to assess the quality of each study. The NOS consists of 3 parts and 9 items: selection (0–4 points), comparability (0–2 points), and outcome assessment (0–3 points). A study with 0 or 1 star in the selection domain or 0 star in the comparability domain or 0 or 1 star in the outcome/exposure domain is considered poor quality, 2 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain are considered fair quality; and 3 or 4 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain are considered good quality. Two investigators (TM and KCG) independently conducted quality assessment, and discrepancies were resolved by a third investigator (GZ).

We analyzed the morbidity of CEs, ADEs and NADEs, NADIs, and NADNIs among the baseline population. CD4 counts were categorized into three and four subgroups to calculate event morbidity (detailed groupings in appendix table S2). We then compared the morbidity risk (OR and 95% CI) of each event in different CD4 subgroups against the normal CD4 range (> 500 cells/μL). All the statistical analyses were performed via R statistical software (version 4.2.0). The random-effects model was used to calculate pooled results and their 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic, and forest plots were generated to visualize specific effect sizes and their 95% CIs for each study. All *p*-values were two-sided, and values less than 0.05 were considered statistically significant.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 11,193 potentially eligible studies, and after the removal of duplicates, 3651 articles were screened for their title and abstract. From this screening, we identified 1576 full-text articles for review (see Fig. 1). After full-text review, 15 studies (15 cohorts) involving 188,945 individuals were included in our meta-analysis.[7,14–27] Of these studies, 2 studies were prospective, 12 were retrospective cohort studies, and only one study contained prospective and retrospective cohorts. All studies were published between 1999 and 2020, and the study periods were all between 1995 and 2017. More than half of the participants in all the studies were male (see Table 1).

The key quality characteristics of the included studies are shown in Table 1 and appendix table S3. The quality of the included studies was relatively high, with NOS scores all above five stars. Most of the included studies were retrospective, and none reported the rate of follow-up loss. In total, 15 studies were included, with 13 related to ADEs,[7,14–21,23–25,27] 10 related to NADEs,[14–19,22–24,26] 9 related to NADNIs,[7,14,15,18,19,22–24,26] and 4 related to NADIs.[7,14,15,18]

We assessed the morbidity rates for ADEs and NADEs in different CD4 count groups. Nine studies involving 34,525 participants reported ADE morbidity rates across three CD4 count thresholds: < 200, 200–500, and > 500 cells/μL. The observed morbidity rates were 24·5% (95% CI: 13·0–38·3), 10·4% (95% CI: 5·00–17·5), and 6·40% (95% CI: 2·30–12·4), respectively. This trend of decreasing ADEs morbidity with increasing CD4 counts was consistently observed across all analyzed groupings (Table 2, Fig. 2, and appendix Fig. S1–S6).

Ten studies with 38,155 participants, focused on NADE morbidity rates across the same CD4 count thresholds. Interestingly, the relationship between CD4 counts and NADE morbidity differed from that observed with ADEs. The morbidity rates for the < 200, 200–500, and > 500 cells/μL groups were 24·2% (95% CI: 10·1–42·0), 29·7% (95% CI: 12·7–50·3), and 28·3% (95% CI: 9·40–52·5), respectively. This pattern, which was consistent across other groupings, suggested that there was no clear association between CD4 counts and NADE morbidity rates (Table 2, Fig. 2, and appendix Fig. S7–S12).

However, a notable exception emerged for very low CD4 counts (< 50 cells/μL), where the NADE morbidity rate was 9·50% (95% CI: 3·40–18·2). This rate was markedly lower than those observed in the 50–200 cells/μL group (31·2%, 95% CI: 8·10–61·1) and the > 200 cells/μL group (37·3%, 95% CI: 8·60–72·3). This trend was consistently observed across all analyzed groupings (Table 2 and Fig. 2).

We further divided NADEs into NADIs and NADNIs, and assessed the morbidity rates in different CD4 count groups. We found that the morbidity rates of patients with NADIs decreased with increasing CD4 count, but there was no clear association between CD4 count and the morbidity rate of patients with NADNIs. See appendix table S4 for details.

We compared the morbidity rates of CEs between groups with poor $CD4^+$ T-cell recovery and those with normal CD4 counts (> 500 cells/μL). ADEs were significantly more common in groups with CD4 counts < 200 cells/μL (OR = 2·68, 95% CI: 2·22–3·23) and 200–350 cells/μL (OR = 1·63, 95% CI: 1·36–1·97) than in the normal CD4 count group. Similarly, NADIs were more prevalent in the < 200 cells/μL group (OR = 2·82, 95% CI: 1·50–5·31) than in the 200–350 cells/μL group (OR = 1·04, 95% CI: 0·65–1·64). Notably, the ADE or NADI rates of the 350–500 cells/μL group were not significantly different from those of the normal group. Interestingly, the prevalence of NADNIs remained consistent across all CD4 count groups, suggesting that their occurrence may be independent of CD4 counts. The detailed results are presented in Table 3, appendix table S4, and appendix Fig. S13–S15.

Discussion

To the best of our knowledge, this meta-analysis represents the first comprehensive evaluation of the morbidity rate of CEs in PLWH with poor $CD4^+$ T-cell recovery following ART. Our analysis revealed

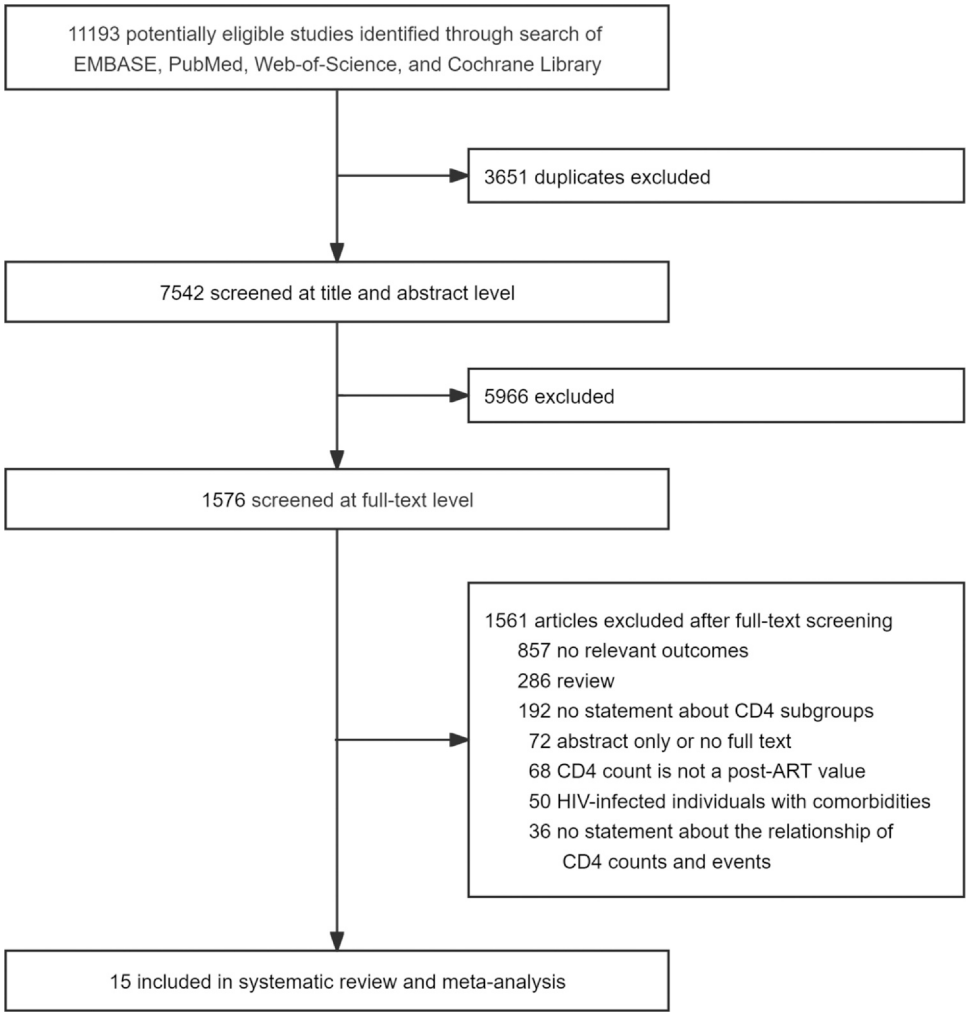

Fig. 1. Study selection. HIV = human immunodeficiency virus. ART = antiretroviral therapy.

that the morbidity of ADEs and NADIs decreases with increasing CD4 cell count, whereas the morbidity of NADNI is not significantly associated with CD4 count. Specifically, individuals with CD4 counts < 200 cells/μL and 200–350 cells/μL presented higher ADE morbidity than those with normal CD4 counts did, with ORs of 7·04 (95% CI: 1·77–28·03) and 1·63 (95% CI: 1·36–1·97), respectively. Similarly, those with CD4 counts < 200 cells/μL had a higher morbidity associated with NADIs (OR = 2·82, 95% CI: 1·50–5·31) than did those in the normal CD4 count group. These findings underscore the importance of understanding the risk of CEs in patients with poor $CD4^+$ T-cell recovery and highlight the need for optimized CD4 count monitoring strategies following ART initiation in PLWH.

The observed inverse relationship between CD4 counts and the morbidity of both ADEs and NADIs aligns with our understanding of HIV pathogenesis and immune function. HIV primarily targets $CD4^+$ T cells, leading to their depletion and subsequent immune system impairment.[28] Our meta-analysis confirmed that as CD4 counts increase, the risk of both ADEs and NADIs decreases, underscoring the critical role of CD4 cells in maintaining immune competence. This finding is consistent with previous studies,[5,29–31] such as the work by Podlekareva *et al*., which demonstrated a strong association between higher CD4 counts and a reduced risk of opportunistic infections in PLWH.[32] Cohort studies have also documented the protective effect of higher CD4 counts against NADIs.[7,14,15] However, to our knowledge, this is the first meta-analysis to provide evidence of the inverse relationships between CD4 counts and the morbidity rates of both ADEs and NADIs.

Our findings reveal a significant increase in the risk of ADEs when CD4 counts were less than 350 cells/μL, and a notable increase in NADIs when CD4 counts were less than 200 cells/μL. These observations offer new insights into the definition of immunological nonresponse (INR). Importantly, there is currently no consensus in the academic community regarding the definition of the INR, with considerable ongoing debate. Some investigators define the INR as CD4 counts remaining below 200 cells/μL after two years of ART,[33,34] whereas others advocate for higher thresholds, such as 350 or even 500 cells/μL.[35,36] Our study supports the use of 350 cells/μL as a critical threshold for the INR, as patients face a significantly increased risk of ADEs at this level. Concurrently, the 200 cells/μL threshold should not be overlooked, as it also markedly increases the risk of NADIs. Consequently, we propose a stratified approach to assess the INR: a CD4 count < 350 cells/μL is defined as the INR, and a value < 200 cells/μL is defined as a severe INR. This stratified definition method not only considers varying degrees of immune function recovery but also directly correlates with clinical risk.

Identifying the two critical thresholds of CD4 count < 350 and < 200 cells/μL has significant implications for guiding clinical strategies in CD4 count monitoring. The current guidelines published by HHS recommend adjusting the monitoring frequency on the basis of CD4 count levels: for patients initiating ART, if the CD4 count is < 300 cells/μL, testing should be performed every 3 months during the first 2 years of viral suppression, and then reduced to every 6 months; if the CD4 count is ≥300 cells/μL, testing should be performed every 6 months, with the frequency potentially further

Table 1
Characteristics of studies included in the systematic review.

	Country	Study design	Study period	Participants (n)	Age (years)	Male (%)	Time of CD4 testing	NOS score	Quality
Sohn AH (2020)[7]	Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam	Retrospective and prospectively cohort	2008–2017	6567	Median: 6-7	52	At cART	7	Good
Croxford S (2019)[14]	England	Retrospective cohort	2016	206	Median: 56	77	At death	7	Good
Croxford S (2017)[15]	England	Retrospective cohort	1997–2012	88,994	≥15	64	At diagnosis	7	Good
Engels EA (2017)[16]	USA	Retrospective cohort	1995–2009	46,956	≥18	83·3	Most recent (after ART)	7	Good
Raffetti E (2015)[17]	Italy	Retrospective cohort	1986–2012	16,268	≥18	74·5	At cancer diagnosis	7	Good
Weber R (2013)[18]	Switzerland	Prospective cohort	1988–2010	9053	≥18	74	At time of death	7	Good
Riedel DJ (2013)[19]	USA	Retrospective cohort	2005–2008	447	Median: 50	79·2	At cancer diagnosis	6	Good
Plettenberg A (2011)[20]	Germany	Retrospective cohort	NS	822	≥14	86·6	At the first event	6	Good
Smurzynski M (2010)[21]	America	Prospective cohort	1996–2008	2948	≥17	82·77	At baseline	7	Good
Belloso WH (2010)[22]	Latin American	Retrospective cohort	1997–2007	6007	≥16	70	At SNA diagnosis	7	Good
Crum-Cianflone N (2009)[23]	USA	Retrospective cohort	1984–2006	4498	Median: 28	91	At first cancer occurrence or last follow-up visit	7	Good
Long JL (2008)[24]	USA	Retrospective cohort	1996–2005	2566	Median: 38	67·6	At cancer diagnosis	7	Good
Moore DM (2006)[25]	Canada	Retrospective cohort	1996–2003	1084	Median: 39·7	88	After HAART	6	Good
Burgi A (2005)[26]	USA	Retrospective cohort	1998–2003	4144	All age stages	90·3	At NADCs diagnosis	7	Good
d'Arminio Monforte A (1999)[27]	Italy	Prospective cohort	1996–1998	585	Median: 34	72·3	After ART	5	Good

Abbreviations: ART = antiretroviral therapy. HARRT = highly active antiretroviral therapy. cART = combination antiretroviral therapy. SNA = serious non-AIDS. NADCs = non-AIDS-defining cancers. NOS = Newcastle-Ottawa Scale.

reduced after 2 years.[3] However, on the basis of our findings, we recommend the following monitoring strategy: patients with a CD4 count < 200 cells/μL (severe INR) should be monitored every three months during the first two years of viral suppression, and every six months thereafter for the next two years. Patients with a CD4 count between 200–350 cells/μL (INR) should be monitored every six months for the first two years and annually thereafter. For patients with a CD4 count > 350 cells/μL, monitoring can be optional, as the morbidity of CEs is similar to that of PLWH with normal CD4 counts. This risk-based stratified monitoring strategy not only considers different degrees of immune function recovery but is also directly related to clinical risk, helping to improve patient management and enhancing the cost-effectiveness of medical resource utilization.

Our meta-analysis revealed no significant correlation between the morbidity of patients with NADNIs and CD4 counts. This finding appears to contradict previous guidelines and the majority of reported results. For instance, Chammartin *et al.* reported in a large cohort study that lower CD4 counts were associated with an increased risk of NADEs, including noninfectious events.[6] Similarly, research by Achhra *et al.* suggested that immunodeficiency was linked to an elevated risk of severe NADEs.[37] A guideline issued by the HHS indicates an association between low CD4 counts and an elevated risk of NADEs.[3] In fact, the occurrence of NADEs, particularly NADNIs, has complex underlying causes. For example, liver and kidney damage are often related to ART medications, whereas diabetes and osteoporosis are frequently associated with drug-induced metabolic issues.[38,39] Furthermore, chronic diseases such as coronary heart disease are linked primarily to patient aging and lifestyle factors.[40] Although these NADEs may all be related to immune dysregulation in patients (e.g., immunosuppression or persistent immune activation), the immune response may not play a dominant role in the pathogenesis of NADNIs. Therefore, while our findings may not align with those of some previous studies, they are nonetheless plausible.

Our study revealed that the morbidity of patients with NADNIs was not significantly correlated with the CD4 count, which has important clinical implications. First, this discovery challenges the traditional practice of relying solely on CD4 count to assess the overall health status of PLWH. With the widespread use of ART, PLWH are living longer and entering an aging phase, which presents new challenges. Guaraldi *et al.* reported that the prevalence of multimorbidity (≥3 chronic diseases) is high among PLWH over 65 years of age.[41] Our findings are consistent with these observations, emphasizing the need for a more comprehensive approach in managing PLWH. Second, this result suggests that clinicians should not focus solely on increasing the CD4 count when developing treatment and prevention strategies but should also consider other factors that may influence the occurrence of NADNIs. A modeling study by Smit et al. predicted that by 2030, non-AIDS-defining cancers and cardiovascular diseases will become the main disease burden for PLWH.[42] Therefore, we recommend incorporating more comprehensive health assessments, including cardiovascular risk assessment, bone density checks, and cancer screenings, into the routine management of PLWH. Furthermore, Althoff *et al.* reported that, compared with HIV-uninfected populations, PLWH experience myocardial infarction, end-stage renal disease, and non-AIDS-defining cancers at earlier ages,[43] further emphasizing the importance of early intervention and prevention.

Our results demonstrated that in patients with extremely low CD4 counts (< 50 cells/μL), the morbidity associated with NADEs was significantly lower than that in patients with higher CD4 counts. This finding does not indicate a reduced morbidity of NADEs in patients with CD4 counts < 50 cells/μL. Rather, it may stem from multiple factors, including survivor bias, more aggressive treatment regimens, and limitations in sample size. Notably, patients with extremely low CD4 counts actually face a very high risk of death and severe

Table 2
Meta-analysis for the morbidity of ADEs and NADEs after ART treatment in different Subgroups of CD4 count.

	ADEs				NADEs			
	Number of studies (n)	Number of Participants (n)	Proportion (95% CI, %)	Heterogeneity (I^2, %)	Number of studies (n)	Number of Participants (n)	Proportion (95% CI, %)	Heterogeneity (I^2, %)
Subgroups of CD4 count (cells/μL)								
$CD4^+$ T-cell count thresholds: 200 and 500								
less than 200	9	13,224	24·5 (13·0, 38·3)	100	10	14,137	24·2 (10·1, 42·0)	99
200–500	9	12,385	10·4 (5·00, 17·5)	98	10	13,579	29·7 (12·7, 50·3)	99
more than 500	9	8916	6·40 (2·30, 12·4)	97	10	10,439	28·3 (9·40, 52·5)	99
$CD4^+$ T-cell count thresholds: 50 and 200								
less than 50	6	2142	50·3 (26·0, 74·4)	99	4	2069	9·50 (3·40, 18·2)	98
50–200	6	4409	24·2 (9·90, 42·4)	99	4	3725	31·2 (8·10, 61·1)	99
more than 200	6	14,809	11·8 (4·40, 22·2)	99	4	13,536	37·3 (8·60, 72·3)	100
$CD4^+$ T-cell count thresholds: 350 and 500								
less than 350	5	10,361	22·6 (8·60, 40·9)	100	5	10,050	30·9 (11·4, 54·8)	100
350–500	5	3897	7·90 (1·20, 19·6)	97	5	3776	37·4 (11·3, 68·4)	99
more than 500	5	6064	11·2 (3·80, 21·9)	98	5	5932	28·8 (8·60, 55·1)	99
$CD4^+$ T-cell count thresholds: 50, 200, and 350								
less than 50	4	2014	53·9 (18·0, 87·6)	100	3	2006	10·0 (2·30, 22·4)	99
50–200	4	4058	27·6 (6·40, 56·6)	100	3	3711	22·2 (3·20, 51·6)	100
200–350	4	4179	17·0 (4·60, 35·1)	99	3	3902	29·9 (1·20, 74·9)	99
more than 350	4	9884	13·6 (3·10, 29·8)	99	3	9357	29·9 (1·50, 73·8)	100
Subgroups of CD4 count (cells/μL)								
$CD4^+$ T-cell count thresholds: 50, 200, and 500								
less than 50	4	2004	44·2 (16·2, 74·4)	100	3	1996	14·7 (1·80, 36·8)	99
50–200	4	4113	19·6 (5·50, 39·8)	100	3	3841	27·7 (1·80, 68·3)	100
200–500	4	8175	10·5 (2·30, 23·6)	99	3	7666	29·0 (1·70, 71·2)	100
more than 500	4	6054	7·80 (1·70, 17·8)	98	3	5759	24·0 (2·30, 58·6)	99
$CD4^+$ T-cell count thresholds: 100, 200, and 500								
less than 100	4	7294	19·7 (2·40, 47·9)	100	3	7217	7·80 (1·30, 19·1)	99
100–200	4	4095	13·2 (1·70, 33·2)	99	3	3892	13·1 (1·90, 32·2)	99
200–500	4	10,471	8·80 (1·10, 22·9)	99	3	9962	13·3 (2·00, 32·5)	100
more than 500	4	6983	6·10 (0·50, 17·3)	98	3	6688	12·4 (1·00, 33·5)	99

Abbreviations: ART = antiretroviral therapy. ADEs = AIDS-defining events. NADEs = non-AIDS-defining events.

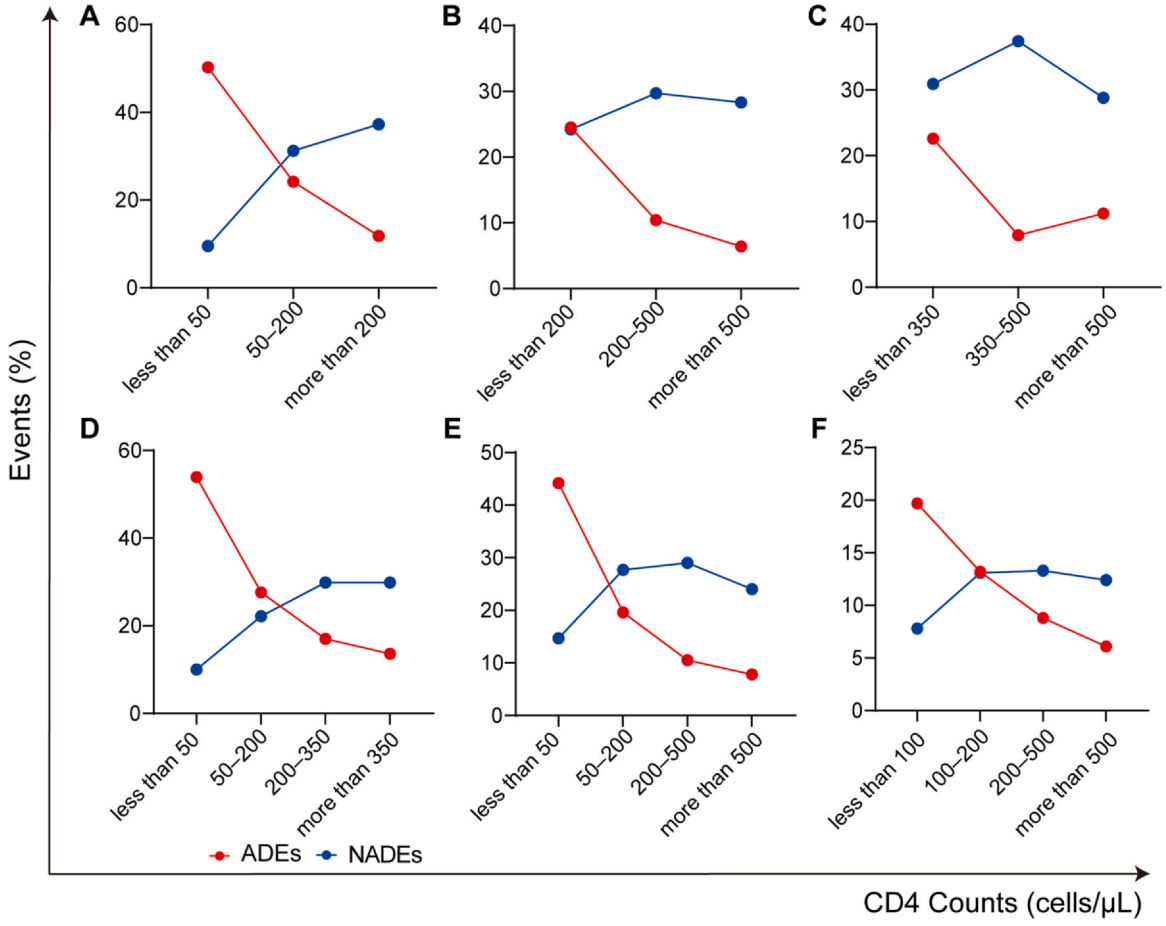

Fig. 2. Distribution of trends in the morbidity of patients with ADEs and NADEs in different CD4 subgroups. The $CD4^+$ T-cell counts were divided into three subgroups: less than 50 cells/μL, 50–200 cells/μL and more than 200 cells/μL; less than 200 cells/μL, 200–500 cells/μL, more than 500 cells/μL; and less than 350 cells/μL, 350–500 cells/μL and more than 500 cells/μL. The $CD4^+$ T-cell counts divided into four subgroups, less than 50 cells/μL, 50–200 cells/μL, 200–350 cells/μL and more than 350 cells/μL; less than 50 cells/μL, 50–200 cells/μL, 200–500 cells/μL and more than 500 cells/μL; and less than 100 cells/μL, 100–200 cells/μL, 200–500 cells/μL and more than 500 cells/μL. ADEs = AIDS-defining events. NADEs = non-AIDS-defining events.

opportunistic infections. Studies have shown that these patients have a significantly increased early mortality rate, with 52% of early deaths being AIDS-related.[37,44,45] Therefore, the seemingly low incidence of NADEs in the data may be obscured by more pressing survival issues.

Our study has several noteworthy limitations. First, despite our comprehensive search strategy, the relatively small number of articles included in the analysis may have limited the representativeness and generalizability of our findings. Second, mortality data were reported in only a few studies, which limited the depth of our analysis of this crucial clinical outcome. Third, our study may be subject to publication bias, where there is a tendency to publish positive or significant results, while negative findings may be underreported. Fourth, significant heterogeneity was observed among the studies, which could be attributed to differences in population characteristics, treatment regimens, follow-up periods, and other factors across studies. Fifth, the included studies did not consider CD4% or the CD4/CD8 ratio, which restricts a comprehensive evaluation of the immune status of the enrolled population. Finally, owing to the lack of specific classification details on ADEs in the included studies, the data presented are insufficient to fully capture the distribution and characterization of these clinical events in HIV-infected individuals.

In conclusion, this meta-analysis reveals a significant inverse relationship between $CD4^+$ T-cell counts and the risk of ADEs and NADIs in PLWH post-ART, with critical thresholds identified at 350 cells/μL and 200 cells/μL, respectively. Our findings support a stratified approach to define the INR: CD4 counts below 350 cells/μL should be considered the INR, whereas counts below 200 cells/μL should be classified as severe INR. Contrary to previous assumptions,

Table 3
Risk of ADEs, NADIs, and NADNIs with poor $CD4^+$ T-cell recovery after ART treatment compared with CD4 counts in the normal range (> 500 cells/μL).

	ADEs (OR, 95%)	NADIs (OR, 95%)	NADNIs (OR, 95%)
CD4 counts (cells/μL)			
< 200 vs. > 500	**7·04 (1·77, 28·03)**	**2·82 (1·50, 5·31)**	0·72 (0·18, 2·81)
200–350 vs. > 500	**1·63 (1·36, 1·97)**	1·04 (0·65, 1·64)	1·06 (0·59, 1·89)
350–500 vs. > 500	1·15 (0·94, 1·41)	1·40 (0·80, 2·46)	1·29 (0·66, 2·53)

Abbreviations: ART = antiretroviral therapy. OR = odds ratio. ADEs = AIDS-defining events. NADIs = non-AIDS-defining infections. NADNIs = non-AIDS-defining noninfections.
Bold values indicate ORs with 95% confidence intervals that do not cross 1, indicating statistically significant associations between the variable and the outcome at the 95% confidence level.

no significant associations were found between CD4 counts and NADNIs. This finding underscores the importance of comprehensive health assessments in the routine management of PLWH, beyond CD4 monitoring, including cardiovascular risk assessment, bone density checks, and cancer screenings.

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Author contributions

YQK and GZ conceived and designed the study, collected the data, performed the formal analysis, curated the data, and wrote and prepared the original draft. TM and KCG collected the data and validated the study. All the authors contributed to the methodology, interpreted the results, contributed to the writing of the manuscript, approved the final version, and had final responsibility for the decision to submit for publication. YQK is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability

Data may be made available by contacting the corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106414.

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