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ORIGINAL ARTICLE

Immune restoration affects 10-year survival in people living with HIV/AIDS

Bogusz Jan Aksak-Wąs[1] | **Justyna D. Kowalska**[2,3] | **Piotr Ząbek**[2] | **Karol Serwin**[1] | **Milena Rafalska-Kosior**[1] | **Joanna Gołąb**[1] | **Daniel Chober**[1] | **Karolina Skonieczna-Żydecka**[4] | **Małgorzata Hackiewicz**[2,3] | **Miłosz Parczewski**[1]

[1]Department of Infectious, Tropical Diseases and Immune Deficiency, Pomeranian Medical University in Szczecin, Szczecin, Poland

[2]Department of Adults' Infectious Diseases, Medical University of Warsaw, Warsaw, Poland

[3]Hospital for Infectious Diseases in Warsaw, Warsaw, Poland

[4]Department of Human Nutrition and Metabolomics, Pomeranian Medical University in Szczecin, Szczecin, Poland

Correspondence
Bogusz Jan Aksak-Wąs, Department of Infectious, Tropical Diseases and Immune Deficiency, Pomeranian Medical University, Arkońska 4 71-455 Szczecin, Poland.
Email: bogusz.aw@gmail.com

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Abstract

Introduction: In recent years, a reduction in the life expectancy gap between people living with HIV (PLWH) and the general population has been observed, irrespective of CD4 lymphocyte count, due to widespread access to antiretroviral treatment. The increase in the life expectancy of PLWH has increased awareness of both the ageing process and gender discrepancies in immune restoration and survival.

Materials and Methods: Longitudinal data were collected for 2240 patients followed up at the Hospital for Infectious Diseases in Warsaw, Poland ($n = 1482$), and the Department of Acquired Immunodeficiency, Pomeranian Medical University, Szczecin, Poland ($n = 758$). Immune restoration was measured from the time of starting combination antiretroviral therapy until achieving 500 CD4 lymphocytes/μL, 800 CD4 lymphocytes/μL, and CD4/CD8 lymphocyte ratios of > 0.8 and > 1.0. Full recovery was achieved when the patient was restored to both 800 CD4 lymphocytes/μL and a CD4/CD8 lymphocyte ratio > 1.0.

Results: For all endpoints, immune restoration had a protective effect by reducing mortality. Patients who achieved immune restoration had a greater chance of reduced mortality than those who did not achieve immune restoration: for CD4 count > 500 cells/μL, HR = 5.4 (interquartile range: 3.09–9.41), $p < 0.001$; for CD4 > 800 cells/μL, HR = 5.37 (2.52–11.43), $p < 0.001$; for CD4/CD8 ratio > 0.8, HR = 3.16 (1.81–5.51), $p < 0.001$; for CD4/CD8 ratio > 1.0, HR = 2.67 (1.49–5.24), $p = 0.001$, and for full immune recovery, HR = 3.62 (1.63–8.04), $p = 0.002$.

Conclusions: Immune restoration remains a powerful factor in improving the survival of PLWH, regardless of the speed of recovery.

KEYWORDS
immune restoration, mortality, PLWHA, survival

INTRODUCTION

HIV belongs to the genus lentivirus in the retrovirus family. This group VI RNA virus (ssRNA-RT) causes AIDS. It most probably evolved from simian immunodeficiency virus [1]. HIV infects cells with CD4 receptors on their surface. These CD4 cells are mainly T-helper lymphocytes, but may also be macrophages,

dendritic cells, microglia, monocytes, eosinophils and thymus cells.

Studies of the natural history of HIV infection have observed that during the first 8 years of follow-up, viraemia increases by 0.04 log copies/mL per year [2]. It has been estimated that the majority of people living with HIV (PLWH) will experience progression of the infection if left untreated. Two special groups of patients, known as 'elite controllers' and 'viraemic controllers', are capable of controlling HIV infection without antiretroviral treatment (ART). Elite controllers maintain an undetectable HIV viral load, despite being infected, and viraemic controllers do not achieve a viral load higher than 50–2000 copies/mL, despite the lack of ART [3]. The typical rate of loss of CD4 lymphocytes during HIV infection is 30–40/μL per year.

The progression of immunodeficiency is inhibited by effective ART. Over the past several decades, the recommendations for ART have changed significantly, from the initial threshold CD4 count of < 200 cells/μL, determined mainly by the toxicity of ART, to < 350 cells/μL in 2010, and <500 cells/μL in 2013. Then, in 2015, the World Health Organization recommended the 'test and treat' strategy, in which each infected individual is treated, regardless of their baseline CD4 lymphocyte levels or HIV load [4].

In recent years, the care of PLWH has been marked by meeting the Joint United Nations Programme on HIV and AIDS 90-90-90 goal. This goal states that, by 2020, 90% of people living with HIV/AIDS should be diagnosed, 90% should be treated with antiretrovirals, and 90% of those on treatment should show viral suppression [5]. In Poland, achieving the second and third 90% goals is improving, but the diagnosis of HIV infection remains a major problem [6].

A reduction in the life expectancy gap between PLWH and the general population has been observed, irrespective of CD4 lymphocyte count, due to widespread access to ART [7]. The long-term survival of people living with HIV/AIDS depends on an array of factors, including, but not limited to, sex, the route of transmission, history of drug use, race, the clinical and immunological status of the patient at the time of HIV diagnosis [8], the amount of delay in presentation into care [9, 10], genetic variants [11–14] and HIV subtype [15]. The higher mortality rate for PLWH may also be affected by the increased prevalence of cancer in PLWH and the time taken to implement ART and type of ART implemented [16].

The largest differences in life expectancy between the general population and people living with HIV people are seen in Africa, particularly in sub-Saharan Africa, where the differences between these populations may be > 10 years [17]. Analyses from developed countries, such as the USA and Canada, suggest, however, a significantly higher average age in people with higher numbers of CD4 lymphocytes [8]. Similar findings have been observed in other regions of the world, including Asia, where both a high baseline CD4 lymphocyte count and immune restoration itself, to a CD4 lymphocyte count > 500/μL and a CD4/CD8 lymphocyte ratio > 0.8 or > 1.0 [18], have been shown to prolong life expectancy in the PLWH.

The increasing life expectancy of PLWH has increased awareness of both the ageing process and gender differences in immune restoration and survival. Currently, more than 50% of PLWH are older than 50 years [19]. This poses a considerable challenge in dealing with both the ageing population and the numerous comorbidities of ageing people.

The primary aim of this study was to assess the effect of immune restoration on the survival of PLWH in the Polish population. We also analysed survival in the context of sex and baseline HIV load.

METHODS

Study population

Longitudinal data were collected from 2240 patients followed up at the Regional Infectious Diseases Hospital in Warsaw, Poland ($n = 1482$), and the Department of Acquired Immunodeficiency, Pomeranian Medical University in Szczecin, Poland ($n = 758$). The study protocol was approved by the Bioethical Committee of the Pomeranian Medical University (approval number BN-001/34/04). Written informed consent was obtained from all participants and the data were fully anonymized before being used in statistical analyses.

The following data were collected: age, sex, date of HIV diagnosis (first positive HIV test, if later confirmed by immunoblotting or a positive test for serum HIV-RNA), date of combined ART initiation, date of death, baseline HIV load and baseline CD4 lymphocyte count. The baseline CD4 lymphocyte count was defined as the first documented result after HIV diagnosis.

Immune restoration was measured from the time point of starting combined ART until achieving 500 CD4 lymphocytes/μL, 800 CD4 lymphocytes/μL and CD4/CD8 lymphocyte ratios > 0.8 and > 1.0. Full recovery was indicated when the patient restoration resulted in both 800 CD4 lymphocytes/μL and a CD4/CD8 lymphocyte ratio > 1.0. Survival analysis was performed until the patient's death or 1 August 2020, whichever occurred sooner. For each patient, immune restoration was estimated over a period of 120 months.

In the survival analysis, effective ART was defined as: (i) undetectable viraemia for the previous 6 months, as indicated by < 50 HIV copies/mL in a molecular test; and (ii) the maintenance of viraemia below this threshold

throughout the observation period. Patients were allowed one excursion outside this threshold each year; that is, one viral load PCR test showing > 200 HIV copies/mL. If a patient had two tests showing a detectable viral load during the same year, they were excluded from further analyses. A total of 1727 patients fulfilled these criteria.

Of the analysed data of 2240 patients, 513 had not developed undetectable viraemia within 6 months of initiation of ART, or had at least two spikes in viral load > 200 copies/mL during any year of the follow-up period.

Statistical analysis

Survival analyses for individual parameters, such as sex, the nadir of the CD4 lymphocyte count, baseline viral load and immune restoration, were performed using a Cox proportional hazards model. Immune restoration was assessed at 120-month endpoints in the following three categories: early immune restoration (< 24 months), delayed immune restoration (> 24 months) and no immune restoration. Patients were divided into two groups: those who achieved immune restoration during the observation period and those who did not. In addition, a log-rank analysis of the Kaplan–Meier estimator was performed for immune restoration up to the 120-month time point.

RESULTS

Patient characteristics

The study group was dominated by men ($n = 1468$, 85.0%) and had a median age of 35 years [interquartile range (IQR): 30–42 years]. The median baseline number of CD4 lymphocytes/μL was 301 (IQR: 107–481). The total observation time for the analysed cohort was 11 039.7 years and 6.39 patient-years.

The number of patients with immune restoration to > 500 CD4 lymphocytes/μL was 1478 (85.6%), whereas 831 (48.1%) patients recovered to > 800 CD4 lymphocytes/μL. Furthermore, 1173 (67.9%) patients had their CD4/CD8 lymphocyte ratio restored to > 0.8, and 834 (48.3%) patients had their CD4/CD8 lymphocyte ratio restored to > 1.0. Full immunoreactivity was achieved by 599 (34.7%) patients.

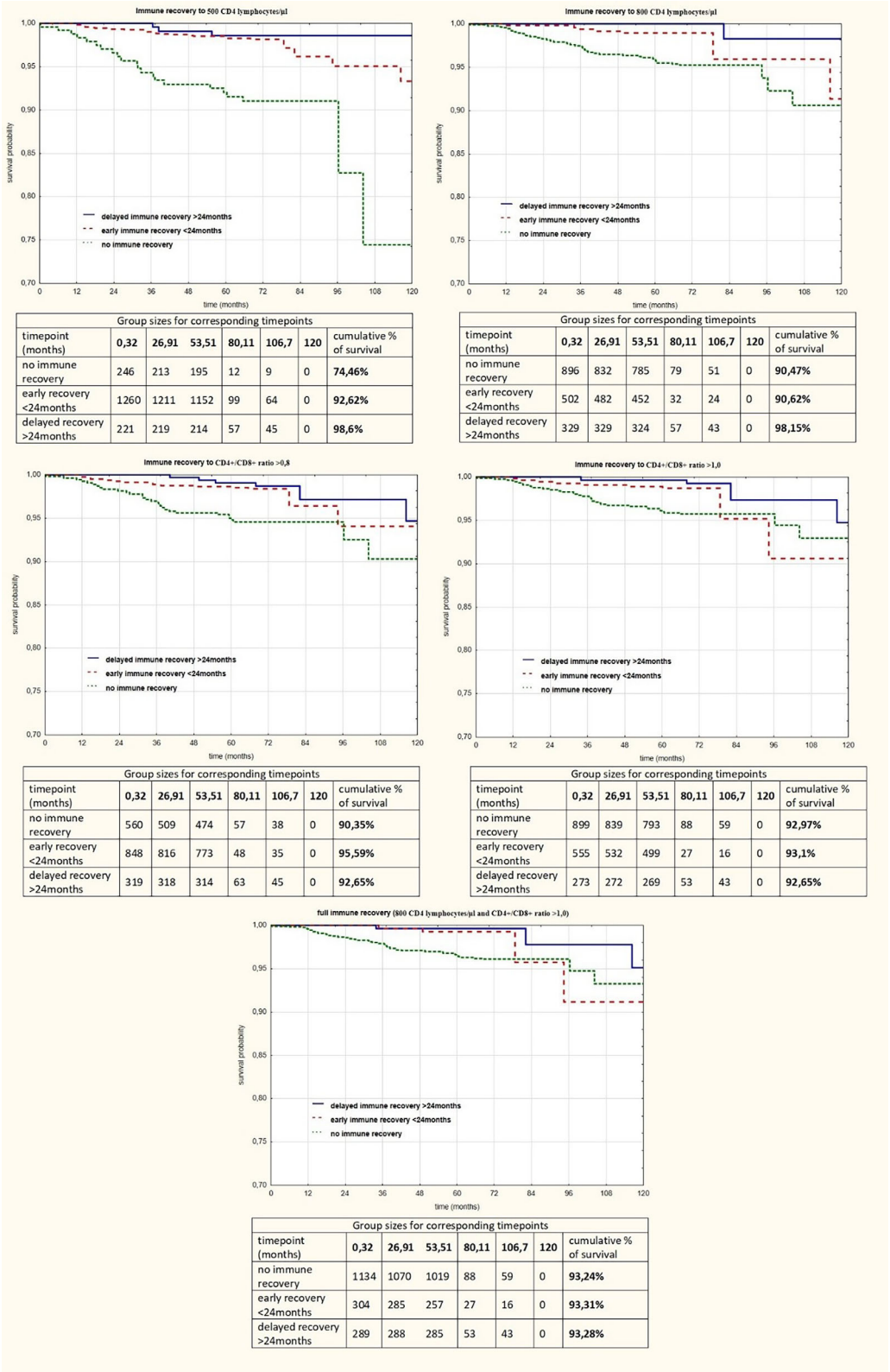
Clinical factors associated with immune recovery

As detailed earlier, survival analysis based on clinical data was performed until the 120-month endpoint (Table 1). Hazard ratios were calculated for the selected variables. Gender had no significant effect on mortality ($p = 0.59$). The median age of the patients at the time of

TABLE 1 The influence of various clinical factors on the mortality of people living with HIV (PLWH) observed for 120 months

	Hazard ratio	*p* (Cox regression)	Lower 95% confidence interval	Upper 95% confidence interval	Number of patients who survived 120 months (Kaplan–Meier estimator)	
Gender (total number of cases = 1727)						
Male	1.25	$p = 0.59$	0.56	2.8	1424 (97.00%)	$p = 0.57$
Female	Ref.				252 (97.30%)	
Age at diagnosis	1.0	$p = 0.41$	1.0	1.0		
CD4 nadir (cells/μL) (total number of cases = 1724)						
< 100	2.52	$p = 0.007$	1.28	4.95	148 (92.50%)	$p = 0.03$
> 100	ref.				1525 (97,51%)	
< 200	3.81	$p < 0.001$	2.16	6.72	310 (92.26%)	$p < 0.001$
> 200	ref.				1363 (98.20%)	
Virological characteristics (total number of cases = 1720)						
Median viral load at diagnosis (log copies/mL)	1.0	$p = 0.9$	1.0	1.0		
Viral load < 5 log copies/mL	ref.	$p = 0.53$	0.62	2.52	1419 (97.26%)	$p = 0.52$
Viral load > 5 log copies/mL	1.25				250 (95.79%)	

Abbreviation: ref., reference.



Group sizes for corresponding timepoints

timepoint (months)	0,32	26,91	53,51	80,11	106,7	120	cumulative % of survival
no immune recovery	246	213	195	12	9	0	**74,46%**
early recovery <24months	1260	1211	1152	99	64	0	**92,62%**
delayed recovery >24months	221	219	214	57	45	0	**98,6%**

Group sizes for corresponding timepoints

timepoint (months)	0,32	26,91	53,51	80,11	106,7	120	cumulative % of survival
no immune recovery	896	832	785	79	51	0	**90,47%**
early recovery <24months	502	482	452	32	24	0	**90,62%**
delayed recovery >24months	329	329	324	57	43	0	**98,15%**

Group sizes for corresponding timepoints

timepoint (months)	0,32	26,91	53,51	80,11	106,7	120	cumulative % of survival
no immune recovery	560	509	474	57	38	0	**90,35%**
early recovery <24months	848	816	773	48	35	0	**95,59%**
delayed recovery >24months	319	318	314	63	45	0	**92,65%**

Group sizes for corresponding timepoints

timepoint (months)	0,32	26,91	53,51	80,11	106,7	120	cumulative % of survival
no immune recovery	899	839	793	88	59	0	**92,97%**
early recovery <24months	555	532	499	27	16	0	**93,1%**
delayed recovery >24months	273	272	269	53	43	0	**92,65%**

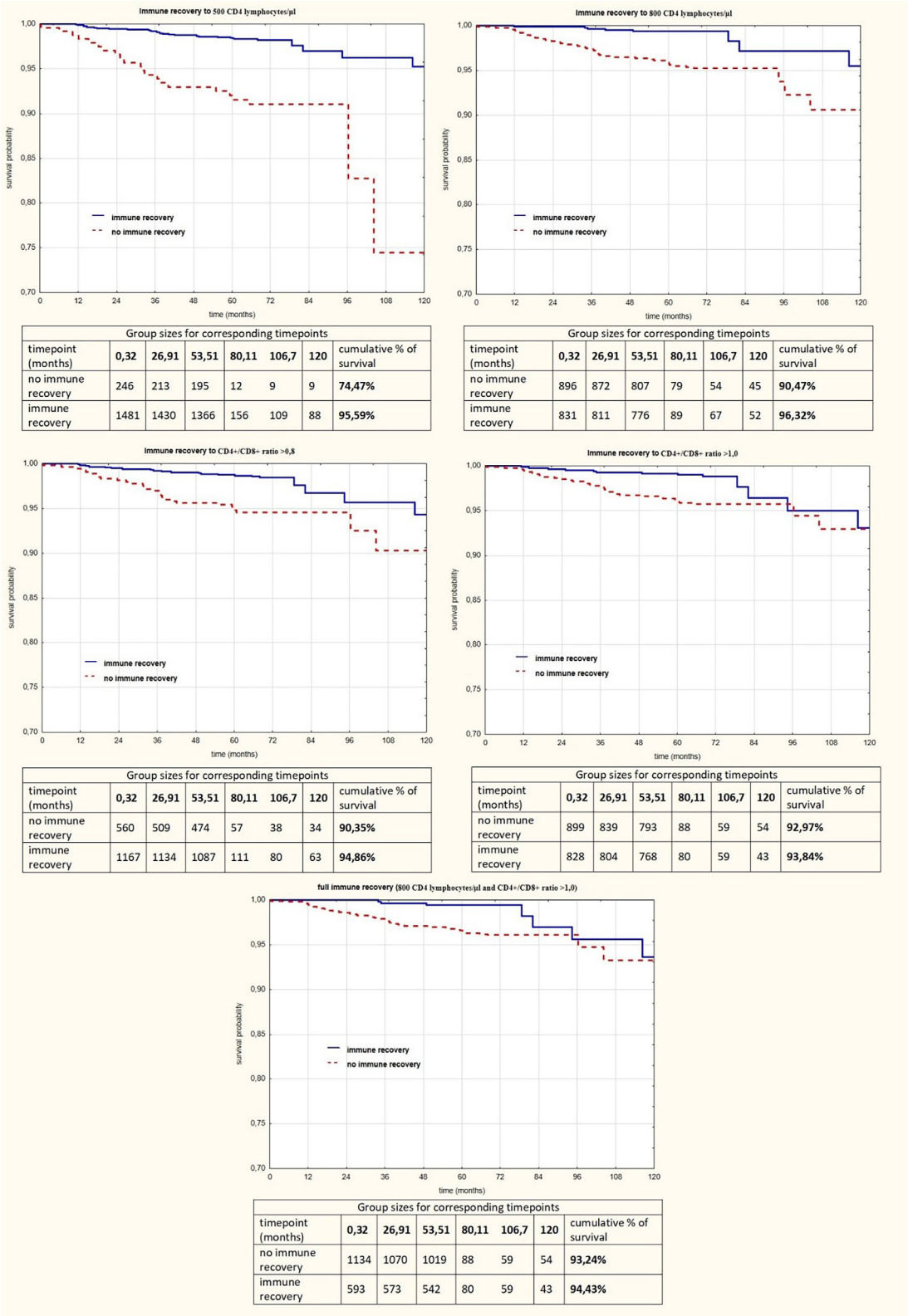
Group sizes for corresponding timepoints

timepoint (months)	0,32	26,91	53,51	80,11	106,7	120	cumulative % of survival
no immune recovery	1134	1070	1019	88	59	0	**93,24%**
early recovery <24months	304	285	257	27	16	0	**93,31%**
delayed recovery >24months	289	288	285	53	43	0	**93,28%**

FIGURE 1 Effect of immune recovery on mortality according to three recovery categories

diagnosis was significantly different between those who survived (mean = 35.0, IQR: 30.0–42.0) and those who did not (mean = 42.0, IQR: 34.0–54.0, $p \leq 0.001$).

The factor that affected mortality was a nadir of CD4 lymphocyte counts in the categories of < 100 and < 200 cells/μL. A lower nadir CD4 lymphocyte count corresponded



Group sizes for corresponding timepoints

timepoint (months)	0,32	26,91	53,51	80,11	106,7	120	cumulative % of survival
no immune recovery	246	213	195	12	9	9	**74,47%**
immune recovery	1481	1430	1366	156	109	88	**95,59%**

Group sizes for corresponding timepoints

timepoint (months)	0,32	26,91	53,51	80,11	106,7	120	cumulative % of survival
no immune recovery	896	872	807	79	54	45	**90,47%**
immune recovery	831	811	776	89	67	52	**96,32%**

Group sizes for corresponding timepoints

timepoint (months)	0,32	26,91	53,51	80,11	106,7	120	cumulative % of survival
no immune recovery	560	509	474	57	38	34	**90,35%**
immune recovery	1167	1134	1087	111	80	63	**94,86%**

Group sizes for corresponding timepoints

timepoint (months)	0,32	26,91	53,51	80,11	106,7	120	cumulative % of survival
no immune recovery	899	839	793	88	59	54	**92,97%**
immune recovery	828	804	768	80	59	43	**93,84%**

Group sizes for corresponding timepoints

timepoint (months)	0,32	26,91	53,51	80,11	106,7	120	cumulative % of survival
no immune recovery	1134	1070	1019	88	59	54	**93,24%**
immune recovery	593	573	542	80	59	43	**94,43%**

FIGURE 2 Effect of immune recovery on mortality according to two recovery categories

to a higher mortality rate [hazard ratio (HR) = 2.52, IQR: 1.28–4.95, $p = 0.007$ for a nadir of < 100 cells/µL; and HR = 3.81, IQR: 2.16–6.72, $p < 0.001$ for a nadir of < 200 cells/µL].

Viral load at the time of diagnosis did not affect mortality in this cohort, either as a continuous variable ($p = 0.9$) or as the categorical variable, lower or higher than 5 log copies/mL ($p = 0.53$).

TABLE 2 Effect of immune restoration (early vs. delayed) to different endpoints on survival of people living with HIV observed for 120 months

	Hazard ratio (risk of death)	p (Cox regression)	Lower 95% confidence interval	Upper 95% confidence interval	Number of patients who survived 120 months (Kaplan–Meier estimator)	
Immune restoration to > 500 CD4 cells/μL						
No immune recovery	4.93	$p < 0.001$	2.79	8.7	224 (91.06%)	$p < 0.001$
Early immune recovery	ref.				1234 (97.94%)	
No immune recovery	9.06	$p < 0.001$	2.65	31.01	224 (91.06%)	$p < 0.001$
Delayed immune recovery	ref.				218 (98.64%)	
Early immune recovery	2.02	$p = 0.26$	0.6	6.78	1234 (97.94%)	$p = 0.22$
Delayed immune recovery	ref.				218 (98.64%)	
No immune recovery	5.4	$p < 0.001$	3.09	9.41	224 (91.06%)	$p < 0.001$
Immune recovery ever observed	ref.				1452 (98.04%)	
Immune restoration to > 800 CD4 cells/μL						
No immune recovery	3.44	$p = 0.002$	1.55	7.66	853 (95.20%)	$p = 0.001$
Early immune recovery	ref.				495 (98.61%)	
No immune recovery	18.57	$p = 0.004$	2.55	135.0	853 (95.20%)	$p < 0.001$
Delayed immune recovery	ref.				328 (99.70%)	
Early immune recovery	7.53	$p = 0.06$	0.9	62.8	495 (98.61%)	$p = 0.03$
Delayed immune recovery	ref.				328 (99.70%)	
No immune recovery	5.37	$p < 0.001$	2.52	11.43	853 (95.20%)	$p < 0.001$
Immune recovery ever observed	ref.				823 (99.04%)	
Immune restoration of CD4/CD8 cell ratio to >0.8						
No immune recovery	3.05	$p < 0.001$	1.64	5.68	530 (94.64%)	$p < 0.001$
Early immune recovery	ref.				833 (98.23%)	
No immune recovery	3.43	$p = 0.006$	1.42	8.27	530 (94.64%)	$p = 0.003$
Delayed immune recovery	ref.				313 (98.12%)	
Early immune recovery	1.28	$p = 0.61$	0.49	3.41	833 (98.23%)	$p = 0.6$
Delayed immune recovery	ref.				313 (98.12%)	
No immune recovery	3.16	$p < 0.001$	1.81	5.51	530 (94.64%)	$p < 0.001$
Immune recovery ever observed	ref.				1146 (98.20%)	
Immune restoration of CD4/CD8 cell ratio to > 1.0						
No immune recovery	2.52	$p = 0.01$	1.22	5.23	861 (95.77%)	$p = 0.01$
Early immune recovery	ref.				546 (98.38%)	
No immune recovery	3.39	$p = 0.02$	1.21	9.53	861 (95.77%)	$p = 0.01$
Delayed immune recovery	ref.				269 (98.53%)	
Early immune recovery	1.99	$p = 0.28$	0.57	6.94	546 (98.38%)	$p = 0.27$
Delayed immune recovery	ref.				269 (98.53%)	
No immune recovery	2.79	$p = 0.001$	1.49	5.24	861 (95.77%)	$p < 0.001$
Immune recovery ever observed	ref.				815 (98.43%)	
Full immune restoration to a CD4/CD8 cell ratio of > 1.0 and ≥ 800 CD4 cells/μL						
No immune recovery	2.89	$p = 0.04$	1.04	8.05	1090 (96.12%)	$p = 0.03$
Early immune recovery	ref.				300 (98.68%)	
No immune recovery	4.43	$p = 0.01$	1.37	14.34	1090 (96.12%)	$p = 0.005$
Delayed immune recovery	ref.				286 (98.96%)	

TABLE 2 (Continued)

Early immune recovery	2.22	$p = 0.31$	0.48	10.21	300 (98.68%)	$p = 0.32$
Delayed immune recovery	ref.				286 (98.96%)	
No immune recovery	3.62	$p = 0.002$	1.63	8.04	1090 (96.12%)	$p < 0.001$
Immune recovery ever observed	ref.				586 (98,82%)	

Note: Total number of cases = 1727. Early immune recovery was defined as immune recovery in < 24 months, after which the patient was regarded as having delayed immune recovery.
Abbreviations: ref., reference.

Survival analysis of immune restoration

For survival analysis, immune restoration was classified as early immune recovery (< 24 months after diagnosis), delayed immune recovery (> 24 months after diagnosis) or no recovery (Figure 1). In addition to these groups, the patients were divided into two groups based on immune recovery and no immune recovery during the observation period (Figure 2).

Immune restoration was defined as an increase in the number of CD4 lymphocytes to > 500/μL or > 800/μL or a CD4/CD8 lymphocyte ratio > 0.8 or > 1.0. Additionally, the composite endpoint of full immune restoration was defined as a CD4/CD8 lymphocyte ratio > 1.0 and > 800 CD4 lymphocytes/μL (Table 2).

Reaching the > 500 CD4 cells/μL endpoint had a statistically significant effect on survival compared with not achieving immune recovery (HR = 5.4, IQR: 3.09–9.41, $p < 0.001$). Furthermore, significantly higher mortality risks were observed when comparing early immune recovery with no recovery and delayed recovery with no recovery (HR = 4.93, IQR: 2.79–8.7, $p < 0.001$ and HR = 9.06, IQR: 2.65–31.01, $p < 0.001$, respectively).

The same association with survival was seen in those who reached the > 800 CD4 cells/μL endpoint (HR = 5.37, IQR: 2.52–11.43, $p < 0.001$) in comparison to those who did not achieve immunorestoration. Furthermore, early immune restoration appears to be beneficial (HR = 3.44, IQR: 1.55–7.66, $p = 0.002$), and for those patients whose CD4 lymphocytes were restored later, this effect on survival was also shown (HR = 18.57, IQR: 2.55–135.0, $p = 0.004$).

Similarly, the mortality risk was significantly lower for those who achieved immune restoration to a CD4/CD8 lymphocyte ratio >0.8 (HR = 3.16, IQR: 1.81–5.51, $p < 0.001$) in comparison to patients without immunoreconstruction, as found in previous analyses both in early restoration (HR = 3.05, IQR: 1.64–5.68, $p < 0.001$) and delayed restoration (HR = 3.43, IQR: 1.42–8.27, $p = 0.006$), with higher death risk for patients who were not immunoreconstructed.

Patients who achieved immune restoration to the CD4/CD8 ratio >1.0 endpoint showed better survival than those without immune recovery (HR = 2.67, IQR: 1.49–5.24, $p = 0.001$). As previously, the same dependency was observed in the early recovery group (HR = 2.52, IQR: 1.22–5.23, $p = 0.01$) and the delayed recovery group (HR = 3.39, IQR: 1.21–9.53, $p = 0.02$).

Full immune recovery remained a statistically significant survival-associated factor when compared with no immune recovery (HR = 3.62, IQR: 1.63–8.04, $p = 0.002$), in both early (HR = 2.89, IQR: 1.04–8.05, $p = 0.04$) and delayed full immune recovery (HR = 4.43, IQR: 1–34, $p = 0.01$) with higher mortality risk in the group no immune recovery.

No statistically significant differences were observed between patients with early and delayed immune recovery during the analysis period.

DISCUSSION

Factors that affect mortality may be divided into clinical factors, such as gender or age; virological factors, such as the HIV subtype [20–22], viraemia at diagnosis and continuous suppression [23, 24]; immunological factors, such as nadir CD4 lymphocyte count or immune recovery; and genetic factors, such as variants in human leukocyte antigen genes [25]and other genes [13]. This study was novel as it was a multi-centre study with a comprehensive analysis of the effect of immune restoration on the survival of PLWH.

Numerous CD4 and CD8 lymphocyte thresholds and ratios have been linked with immune recovery, with no consensus definition on which parameters are most suitable to reflect the immune response to ART. A CD4 lymphocyte count of 500 cells/μL has traditionally been used as a target point for immune restoration. This target is a direct result of the historical division into immunological categories, as suggested by the Centers for Disease Control and Prevention as early as 1993 [26]. However, several guidelines use a CD4 lymphocyte immune recovery threshold of > 800 cells/μL as reflective of more complete immune recovery [27]. This revised target is also associated with a lower risk of cardiovascular disease-related

deaths and it has been assessed in other studies of immune restoration [28, 29]. Furthermore, a CD4/CD8 cell ratio > 1.0 was used, as it has been observed in uninfected individuals and is considered to represent a complete immune response, whereas a CD4/CD8 cell ratio > 0.8 is an intermediate recovery value. In the Aquitaine cohort, this ratio was associated with a lower risk of bacterial infection in PLWH [30].

Our analysis showed a significant reduction in mortality in patients with immune restoration compared with those who were not immunoreactive. Immune restoration to values of 500 and 800 CD4 cells/μL had the greatest effect on the survival of PLWH. We found a more than five-fold decrease in mortality in patients whose CD4 lymphocyte counts were > 500 cells/μL or 800 cells/μL. Meeting the CD4/CD8 lymphocyte ratio threshold showed less of a protective effect, with a two-fold (for a ratio > 1.0) to three-fold (for a ratio > 0.8) reduction in mortality risk. Individual protective values showed considerable variability, in some cases reaching an 18-fold decrease in the risk of mortality (immune restoration up to 800 CD4 cells/μL over 24 months of observation). However, during the course of the analysis, no significant differences were found between patients who achieved immune restoration in < or > 24 months.

These data are consistent with those from previous studies, which have demonstrated improved survival in HIV-positive individuals who achieved immune restoration [31, 32]. In one of these previous studies in a cohort of approximately 10 000 patients from Kampala, Uganda, it was found that a CD4 lymphocyte count of < 100 cells/μL after 1 year on ART and a CD4 lymphocyte count less than the count at baseline were associated with a significantly higher mortality rate. Similar results were obtained in a study of a northern Italian cohort with a sample of approximately 10 000 patients, in which participants before and after the highly active ART era were compared. A significantly lower nadir CD4 lymphocyte count and a higher mortality rate were observed in PLWH before the highly active ART era.

In addition to immune restoration, the CD4 lymphocyte count nadir was also associated with mortality, as patients with a nadir CD4 lymphocyte count of < 100 or < 200 cells/μL showed a greater than two-fold or three-fold increased risk of mortality, respectively. This finding is consistent with those from studies in other cohorts that demonstrated an association between HIV status and baseline CD4 lymphocyte count and an increased risk of mortality [18, 33, 34].

Viraemia at the entrance to care, both as a continuous variable and as a categorical variable based on higher and lower than 5 log copies/mL, did not significantly affect the mortality of PLWH. This was in contrast to the findings of other studies, in which baseline viraemia was found to be a prognostic factor for both the course of infection and mortality [35–37]. It is worth noting that, in this study, the effect of baseline viraemia on mortality was only investigated at the end of the 10-year period. The effect of HIV viral load on the course of infection and on mortality during the subsequent observation period was not studied, which most probably contributed to the differences in the results for different cohorts.

CONCLUSIONS

Immune restoration remains a powerful factor for improving the survival of PLWH, regardless of the speed of recovery. Due to the ageing of the PLWH population, an increasing number of highly effective ARTs, and the increasing clinical observation of patients, acquiring immune restoration is an achievable goal in the care of PLWH. A properly functioning immune system has an undeniable effect on the progression of disease and the survival of patients. However, there remains a lack of large multi-centre studies that would allow for a better understanding of the immune restoration process and its influencing factors. In the future, an in-depth analysis of the effects of various clinical and genetic factors on immune restoration is necessary.

Study limitations

This study has some limitations that should be noted. First, the cohort was 100% Caucasian. Therefore, these findings may not be applicable to other ethnic groups. Second, our analyses may only be relevant to the Polish context, especially regarding access to and the quality of care for PLWH, and they may not apply to countries with different standards [38]. Third, not all factors were available for evaluation at baseline. In our cohort, there were no data available regarding the route of HIV infection or some virological data, such as HIV-1 subtype. Fourth, we did not analyse the relationship between immune recovery, ART components and mortality; however, as shown in other cohorts, the ART components do not have a significant effect [39]. Finally, as in all survival analyses, there is a possibility of statistical bias due to patients lost to follow-up who may have died without the centre's knowledge. Moreover the causes of deaths were also not specified; for some patients these causes were unknown, so it is impossible to draw any far-reaching conclusions on their basis.

AUTHOR CONTRIBUTIONS

BJA-W: writing (original draft), visualization and formal analysis. JDK: data curation and supervision. PZ: formal

analysis and resources. KS: formal analysis and resources. MR-K: data curation and validation. JG: data curation and methodology. DC: methodology and validation. KS-Ż: formal analysis and project administration. MH: data curation and project administration. MP: supervision, writing (original draft) and visualization.

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CONFLICT OF INTEREST

None of the authors have a conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Basic data used for the calculations are available on request from the first author of the manuscript.

ORCID

Bogusz Jan Aksak-Wąs https://orcid.org/0000-0003-2092-3737
Justyna D. Kowalska https://orcid.org/0000-0003-1166-4462
Daniel Chober https://orcid.org/0000-0002-6775-4152

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