Early Treatment of Primary HIV Infection Is Associated with Decreased Mortality

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Abstract

The aim of this study was to understand factors associated with increased mortality in a cohort of primary HIV infection (PHI) in New South Wales (NSW) over three decades. Six hundred and two patients with PHI were enrolled from 1984 to 2009. Probabilistic data linkage was performed to NSW Registry of births deaths and marriages and Australian Bureau of Statistics mortality database. Mortality was measured by crude death rate. Pre highly active antiretroviral therapy (pre-HAART) era was defined as before January 1, 1997. A Cox proportional hazard model was used to identify factors associated with death. One hundred and thirty-eight deaths occurred during 6,223 person years (PY) follow-up. Overall crude death rate was 2.2 per 100 PY (95% confidence interval [CI], 1.9–2.6), 3.6 (95% CI, 3.1–4.3) in pre-HAART era and 0.20 (95% CI, 0.08–0.47) in post-HAART era. AIDS was the most frequent cause of death (52%, 72/138), all occurring in the pre-HAART era. Of non-AIDS deaths, the leading known cause was non-AIDS cancer 8% (11/138) followed by suicide 4% (6/138). On multivariate analysis, estimated date of infection in pre-HAART era and time to commencement of ART greater than 1 year post diagnosis were more likely to be associated with death ($p < .05$). Mortality in PHI has decreased significantly in the post-HAART era. Non-AIDS deaths due to malignancy and suicide are emerging as leading causes in this population in the post-HAART era. Time to starting ART greater than 1 year was associated with increased mortality.

Keywords: HIV, seroconversion, mortality

Introduction

PRIMARY HIV INFECTION (PHI) is the earliest clinical stage following acquisition of HIV and may be characterized by a seroconversion illness.¹ Severity of symptoms during PHI can be associated with disease progression and death.^{2,3} It is a critical time for the establishment of the viral reservoir and host immune response. Cohort studies of PHI can provide insights into the natural history of HIV; however, diagnosing patients at this early stage is challenging as seroconversion may be transient and have a nonspecific clinical presentation. Other cohort studies of PHI have demonstrated the impact of early treatment in delaying disease progression.^{4,5}

Mortality rates were highest before the availability of highly active antiretroviral therapy (HAART) in 1997. In this pre-HAART era, there were no effective treatment options to prevent the progression to AIDS and death. The early HAART era from 1997 to 1999 involved treatment with mono or dual therapies that had short lived efficacy. Only in the late HAART

era, after 2000, were combination regimens with less toxicity widely available.

Large international cohorts have shown decreases in mortality [1.33–1.75 per 100 person years (PY)] and changing causes of death in the post-HAART era.^{6,7} Although life expectancy in Australia has increased for people living with HIV, mortality in the post-HAART era was still ten times greater than the general population.^{8,9} Mortality in PHI within the first 5 years of acquisition approximates the general population, but is increased as the duration of infection increases.¹⁰ As the population diagnosed with PHI is also shifting, with increased community based testing, understanding of disease outcomes in this unique group will be more challenging to determine.

We evaluated mortality rates and causes of death within a New South Wales (NSW) based Australian cohort of PHI over three decades spanning several eras of HIV treatment.

Materials and Methods

We established a cohort of patients with PHI from several randomized clinical trials and prospective observational

cohorts. Participants were enrolled through primary health clinics and hospitals in New South Wales and Victoria from 1984 to 2009, with active follow-up until 31 December 2013. PHI and estimated date of infection (EDI) were defined using strict laboratory criteria, details of these trials and eligibility criteria are published elsewhere: SAPS,¹¹ VIRAX,^{12,13} SPARTAC,¹⁴ PULSE,^{15,16} QUEST,¹⁷ AGOURON,¹⁸ and CORE01.¹⁹ Acute infection was defined in study protocols as either (i) signs and symptoms of acute retroviral symptoms with the presence of positive p24 antigen/HIV-1 proviral DNA/HIV-1 RNA or (ii) indeterminate or evolving Western blot with positive p24 antigen/HIV-1 proviral DNA/HIV-1 RNA. Early stage infection was defined as positive enzyme linked immunosorbent assay and Western blot with a negative documented serological test within 6 months. Data collection was through clinical trial case record forms, centralized into the primary combined united database (PCUD). Consent for usage of data for future studies was obtained from original study protocols.

The main outcome measures were death and cause of death. Deaths were categorized according to the causes of death in HIV (CoDe) protocol²⁰; AIDS defining conditions assigned according to CDC.²¹ Deaths were recorded using original study protocols, with both written and verbal confirmation from treating physicians. To capture any missed deaths due to loss of follow-up, probabilistic data linkage was performed with the NSW Registry of Births, Deaths and Marriages (RBDM) and Australian Bureau of Statistics (ABS) Mortality Data by the NSW Centre for Health Record Linkage.²² ABS mortality database only extended until 2007; hence, to minimize ascertainment bias, the RBDM was also used to capture deaths that may have occurred until census date of December 31, 2013. Identifiers used for linkage were two by two name code, date of birth, and sex.

Crude death rate was calculated using the Poisson exact method with 95% confidence intervals (CIs) reported. Where lower CI was zero, one-sided 97.5% CI was used. Person years of follow-up (PYFU) were EDI until death or last recorded date of follow-up.

A Cox proportional hazard model was used to identify factors associated with death. Univariate analysis was performed on the following categorical variables: sex, time period of enrolment (1986–1996 and 1997–2006), stage of infection (Acute or Early as defined above), number of PHI symptoms, time to start treatment, and first regimen and continuous variables: age at PHI, CD4 count at PHI (expressed per 20 cells/mL), and percent CD4 change per year. Post-HAART era was defined as EDI after January 1, 1997. Number and duration of PHI symptoms were included as continuous variables. Covariates were included in a multivariate model if they had a *p*-value of <.05 in the univariate analysis. The multivariate model was determined using a stepwise approach with a two-sided statistical significance (*p* < .05). Kaplan–Meier method was used for survival analyses. Analyses were performed using STATA (version 14; StataCorp LP, College Station, TX) and SAS (version 9.3; SAS Institute, Inc., Cary, NC). Written informed consent was obtained for original study participants. A waiver of consent was obtained for data linkage. Ethics approval was granted by the NSW Population and Health Services Research Ethics Committee (NPHSREC: HREC/13/CIPHS/60).

Results

There were 667 participants in the PCUD cohort; 602 were NSW residents eligible for data linkage and included in these analyses. There was a total of 6,222 PYFU (3,667 in the pre-HAART and 2,555 in post-HAART period). The median age at PHI diagnosis was 33 years [interquartile range (IQR) 28–39], with a median 9 (IQR 5–13) PYFU. The median baseline CD4 count was 560 cell/mm³ (IQR 396–744), 99% of participants were male, and 81.7% received antiretroviral therapy at any time. Before linkage, there were 105 known deaths.

Mortality

In total, there were 138 deaths confirmed through study protocol or data linkage. Overall crude death rates were 2.2 per 100 PY (95% CI, 1.9–2.6). For those that acquired PHI in the pre-HAART era, mortality was 3.6 per 100 PY (95% CI, 3.1–4.3) compared with 0.20 per 100 PY (96% CI, 0.08–0.47) in the post-HAART era. After 5 years of follow-up, there were 38 deaths, with 481 patients remaining at risk. The cumulative hazard was 0.07 [lower confidence interval (LCI)–upper CI (UCI) 0.0533–0.099]. At 9 years follow-up, there were 99 deaths, with 305 patients remaining at risk. The cumulative hazard was 0.22 (LCI–UCI 0.18–0.27). There has been a decrease in death rate over time, with only five deaths occurring in the post-HAART era group (Fig. 1).

On univariate analysis, those enrolled into a study cohort between the years of 1984 and 1998 had a significantly increased risk of death. Time to starting treatment beyond 1 year also had a significantly increased risk of death. Factors associated with reduced hazards for death include acquiring PHI in the post-HAART era, presence of PHI symptoms, and starting a protease inhibitor containing regime compared with mono or dual nucleoside reverse transcriptase inhibitor/non-nucleoside reverse transcriptase inhibitor based treatment as first regimen (Table 1). There was no significant difference in death rate based on gender (*p* > .20), baseline CD4 count, or rate of change of CD4 count per year.

On multivariate analysis, acquiring PHI in the post-HAART era had a significantly decreased risk of death [hazard ratio (HR) 0.192, 95% CI (0.0671–0.550), *p* = .002]. Stage of infection approached significance and was associated with increased risk of death for early or unknown compared to acute stage of infection [HR 1.26, 95% CI (0.609–2.59) and HR 1.99, 95% CI (1.08–3.65), respectively, overall *p* = .040]. Time to starting antiretroviral therapy beyond 1 year conferred an increased risk of death [HR 2.9, 95% CI (1.42–5.9), *p* = .003], as did a mono or dual nucleoside containing first regimen.

Cause of death

The most frequent cause of death was AIDS (*n* = 72, 52%), malignancy (*n* = 11, 8%), and suicide (6, 4%). Thirty deaths (22%) were classified as unknown. Of the remaining 18 deaths, causes included accident (*n* = 4, 2.9%), substance abuse (*n* = 3, 2.17%), ischemic heart disease and digestive system disease (*n* = 2, 1.45% each), unclassifiable respiratory disease, renal failure, liver failure, infection, central nervous system disease, and chronic viral hepatitis (*n* = 1, 0.72% each). In the pre-HAART era, the majority of deaths were AIDS related, while in the post-HAART era, the number of

FIG. 1. Crude death rate per 100 person years. 95% CI is shown. Where lower CI was zero, one sided 97.5% CI was used with arrows indicating extension beyond axis. CI, confidence interval.

AIDS related deaths decreased, non AIDS cancer and other causes predominated (Fig. 2).

Discussion

This is the first study to report long-term mortality outcomes in an Australian cohort recruited at the time of PHI, and due to the challenging nature of recruiting at the time of PHI, is unlikely to be replicated. Overall, mortality in this cohort has decreased over three decades, in keeping with mortality rates in comparable observational cohorts.⁸ The highest death rates were seen in those recruited before 1998, which coincides with the pre-HAART era, and also in the SAPS study, which recruited almost exclusively during this time period.

In addition, time to starting antiretroviral treatment was an important predictor of death, with delays beyond 1 year resulting in a greater than five times risk of death compared to starting treatment within a year of acquiring HIV. In the setting of PHI, this is a notable finding, as it suggests that the impact of early treatment is related to more than just the CD4 T cell count, a surrogate of immune deficiency. This study suggests that a longer duration of untreated viral replication at the earliest stage of infection has an impact on all-cause mortality, regardless of immune function. Even though large international randomized trials now also conclusively recommend early treatment, these studies were conducted on participants with a median time of 1 year from diagnosis and compared starting immediately versus when the CD4 count fell below 350 cells/mm.²³ These data support the current WHO recommendations of Test and Start and presents an even more compelling argument for early treatment as it is from a cohort of PHI.²⁴ In addition, the advantages of early treatment during PHI, a time of peak viremia, bolster the public health argument of prevention of transmission, thus also aligning with the UNAIDS 90–90–90 targets for epidemic control.²⁵

In this cohort of PHI, recruited at the earliest time point in the natural history of infection, CD4 counts are relatively

preserved, suggesting that treatment has other effects beyond simply preservation of immune function. Although long-term longitudinal CD4 data were not complete in this cohort, analysis of CD4 change within the first year was performed and not found to be significantly associated with death. Acute stage of infection was associated with decreased death compared to early stage and may be related to a greater proportion of earlier treatment in this group (71% vs. 46% started treatment within 1 year). This variable was confounded by a high proportion of unknown stage, which when investigated further was found to contain a greater proportion of earlier years of infection, who delayed treatment initiation beyond 2 years, and hence had a higher hazard ratio for death. To date, the long-term effects of treatment started during primary HIV have been conflicting, with some studies demonstrating immunological benefits, while others suggesting that toxicity of long-term treatment outweighs the benefit of starting early. This study supports current clinical and public health directives for earlier treatment in the primary infection cohort.

A number of factors were significantly associated with a decreased risk of death, including the type of regimen (protease inhibitor containing compared nucleoside only) and the number and severity of symptoms during PHI. The later observation is in contrast to that reported in Vanhems *et al.*³ in a similar but smaller cohort, which suggested a dose–response relationship between severity of PHI infection and a faster rate of disease progression. The median duration of follow-up in that study was only 3 years and was performed in the pre-HAART era.³ This study was much larger and included a broader range of treatment eras, with three times longer median follow-up. Reporting bias due could have resulted in a greater proportion without symptoms in Cohort 1 compared to 2 as Cohort 1 relied on a self-administered questionnaire. In addition, the confounding may have contributed to this finding, as those with more symptoms started treatment earlier.

Cause of death in PHI has changed from predominantly AIDS related to non-AIDS related with malignancy and

TABLE 1. COX PROPORTIONAL HAZARD MODEL OF RISK OF DEATH IN PRIMARY HIV INFECTION STUDIES
IN NEW SOUTH WALES

Variable	n	Univariate analysis					Multivariate analysis				
		Hazard ratio	p Value	Lower CI	Upper CI	Overall p	Hazard ratio	p Value	Lower CI	Upper CI	Overall p
Time period						<.001					.002
1986–1996	306										
1997–2006	296	.044	<.001	0.0181	0.109		0.192	.002	0.0671	0.550	
Stage of infection						<.001					.04
Acute	230										
Early	149	1.9	.07	0.94	3.9		1.26	.5	0.609	2.59	
Unknown	223	7.6	<.001	4.4	13.4		1.99	.03	1.08	3.65	
Number of symptoms	Freq.					<.001					
No symptoms	149										
1–5 Symptoms	220	.47	<.001	0.32	0.70						
6–10 Symptoms	219	.43	<.001	0.28	0.65						
>10 Symptoms	11	.37	.2	0.090	1.51						
Missing	3	<.001	1	<0.001	.						
Time to start treatment						<.001					.002
≤1 year	281										
1–2 years	51	5.6	<.001	2.8	11.1		2.9	.003	1.42	5.9	
>2 years	158	7.7	<.001	4.5	13.3		2.6	.001	1.48	4.7	
Missing	112	4.2	<.001	2.2	7.9		<0.001	<.001	<0.001	<0.001	
First regimen						<.001					.001
Mono or dual	160										
Protease inhibitor ^a	227	.088	<.001	0.048	0.162		0.51	.06	0.251	1.04	
Other ^b	105	.127	<.001	0.061	0.261		0.243	<.001	0.116	0.51	
No treatment	35	<.001	1	<0.001	.		<0.001	1	<0.001	.	
Missing	75	.59	.02	0.38	0.92		.	.	.	.	
Age at PHI	602	.98	.09	0.96	1.00	<.20					
CD4 at PHI	454	1.01	.4	0.99	1.02	0.4					
CD4 PCPY ^c	251	1.05	.2	0.97	1.14	0.2					

^aProtease inhibitor included as part of HAART.

^bIncludes other combination regimens containing integrase inhibitors and non-nucleoside reverse transcriptase inhibitors.

^cCD4 change expressed as percent per year (PCPY).

PHI, primary HIV infection; HAART, highly active antiretroviral therapy; CI, confidence interval.

suicide as leading causes of death in the post-HAART era. This is consistent with findings in other large cohorts that show non-AIDS related malignancies and suicides as prominent causes of death,^{26–28} but this is the first to our knowledge to demonstrate this in the context of people identified at primary infection. A large proportion of causes

of death were listed as unknown. This occurred exclusively in those with PHI from 1985 to 1991 and was due to these participants not linking to any death registry. Possible reasons for not linking may be due to acquiring PHI at a time of intense fear and social stigma around HIV and AIDS. As a result, incorrect identifiers (name code, DOB, and postcode)

FIG. 2. Cause of death over time.

may have been provided to researchers, which restricted the ability to link to official death registries. Alternate reasons could be that despite living in NSW, these participants may have been from interstate, and when faced with deteriorating health and no available treatment options at that time, they may have returned to their state of origin before death. When these unknown deaths were analyzed, all but 1 of 30 had a diagnosis of AIDS before death, making it probable that in an era of no effective treatment for HIV, AIDS was the cause of death.

The availability of antiretroviral treatments over time has had a direct impact on survival in HIV. Initially regimens were limited to monotherapy or dual therapy. Delays in starting treatment may have been due to no available treatments in the pre-HAART era, a potential for confounding. However, our cohort also included clinical trials where early antiretroviral regimens were included in the protocol. Univariate analysis was performed by study type, and this was not found to be significant in relation to mortality. Another limitation of this study was that the entire treatment history, including treatment interruptions, was incomplete, and therefore, only the first treatment regimen was included for this analysis. Viral load suppression at 1-year posttreatment was analyzed as a surrogate measure for treatment adherence and not found to be associated with death. Treatment interruptions are known to be inferior to continuously administered HAART; however, interruptions after commencing first regimen were not analyzed in this study.²⁹ While treatment with efavirenz has been associated with increased risk of suicide, this was not identified in this cohort.³⁰

Other considerations in interpretation of this retrospective cohort study are potential survivor bias from those that remained alive until the availability of combination antiretroviral therapy. This may account for the marked decreased mortality in the post-HAART era. Coinfection such as Hepatitis C was not analyzed, as the serostatus for this variable within the cohort was incomplete. Other important behavioral factors related to mortality were not a part of this study, such as cigarette smoking and intravenous drug usage. Within these limitations, the study findings are consistent with international cohort studies on HIV mortality and causes of death. PHI provides a cohort which is more generalizable than other HIV observational cohorts as all participants are enrolled at the earliest time of HIV acquisition, allowing accurate measurement of time of infection.

In summary, death rates in PHI have decreased significantly over time. Delaying antiretroviral treatment beyond 1 year was associated with increased risk of death. AIDS related mortality was a leading cause of death in pre-HAART era, replaced now by malignancy and suicide as leading causes of death in this cohort.

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Author Disclosure Statement

No competing financial interests exist.

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