

High Mortality Among Human Immunodeficiency Virus (HIV)-Infected Individuals Before Accessing or Linking to HIV Care: A Missing Outcome in the Cascade of Care?

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Background. The “cascade of care” displays the proportion of individuals who are infected with human immunodeficiency virus (HIV), diagnosed, linked, retained, on antiretroviral treatment, and HIV suppressed. We examined the implications of including death in the use of this cascade for program and public health performance metrics.

Methods. Individuals newly diagnosed with HIV and living in Calgary between 2006 and 2013 were included. Through linkage with Public Health and death registries, the deaths (ie, all-cause mortality) and their distribution within the cascade were determined. Mortality rates are reported per 100 person-years.

Results. Estimated new HIV infections were 680 (543 confirmed and 137 unknown cases). Forty-three individuals, after diagnosis, were never referred for HIV care. Despite referral(s), 88 individuals (18%) never attended the clinic for HIV care. Of individuals retained in care, 87% received antiretroviral therapy and 76% achieved viral suppression. Thirty-six deaths were reported (mortality rate, 1.50/100 person-years). One diagnosis was made posthumously. Deaths (20 of 35; 57%) occurred for individuals linked but not retained in care (6.93/100 person-years), and 70% were HIV-related. Mortality rate for patients in care was 0.79/100 person-years. Retained patients with detectable viremia had a death rate of 2.49/100, which contrasted with 0.28/100 person-years in those with suppressed viremia. Eight of these 15 deaths (53%) were HIV-related.

Conclusions. Over half of deaths occurred in those referred but not effectively linked or retained in HIV care, and these cases may be easily overlooked in standard HIV mortality studies. Inclusion of deaths into the cascade may further enhance its value as a public health metric.

Keywords. accessing care; Canada; cascade of care; HIV/AIDS; mortality.

The “human immunodeficiency virus (HIV) treatment cascade” or “cascade of care” has recently been developed as a means to present, as a continuum, the number

of individuals within a population who are infected with HIV, diagnosed with HIV, linked to and retained in HIV care, on treatment, and have achieved suppression of HIV replication [1–6]. The cascade represents a “powerful image” that visualizes the discrete stages along the infected individual’s care continuum [2]. It reflects the steps needed to improve an individual’s HIV health as well as identifies areas of opportunity within a population for interventions to optimize disease management and reduce ongoing HIV transmission. Delays in diagnosis, poor engagement, and inconsistent retention in HIV care have all been shown to negatively impact both individual and public health outcomes [7–11]. Because immense personal and societal benefit could be generated by improving the proportion of

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patients in the later stages of the cascade, it is being used as a performance metric for national or local HIV/acquired immune deficiency syndrome (AIDS) programs. Initial studies showed that only 19% to 25% of all HIV-infected individuals (both aware and unaware of their diagnosis) in the United States have achieved viral suppression, which is the goal of care for most HIV patients in the cascade [1, 12]. In British Columbia, Canada, similar low levels of viral suppression rates were reported at 34.6% in 2011 [3].

Because the cascade of care was primarily designed to follow an individual's lifetime care continuum, it does not include death as a separate marker. However, such an endpoint might be extremely important if the cascade is being used as a program performance metric. For most HIV cohort studies, death is followed only after the individual has entered and been retained in a cohort, and in some cohorts this occurs only after they have started HIV treatment [13–16]. Late presentation (ie, low CD4 count at diagnosis), AIDS comorbidity, delayed access to antiretroviral therapy (ART), incomplete or nonadherence to ART, interruption of retention in care, and comorbidities along with lifestyle issues have all been reported to be associated with increased HIV-related morbidity [17–22]; however, these metrics are usually only determined after an individual accesses HIV care. High-mortality rates associated with lack of access to resources and HIV care has been better described in the developing world [23–25]. Relating death to the cascade has not been undertaken in the developed world; its inclusion might offer insight into areas for program improvement.

We wanted to position all deaths of individuals newly diagnosed with HIV since 2006 living in Calgary and the surrounding areas within the cascade of care. We then wanted to determine how the inclusion of death might identify areas for potential improvement in local care as well as impact the metrics of HIV program performance. Our population is well positioned to examine deaths within the cascade of care because it is covered by a single jurisdiction (ie, Alberta Health Services) and a single provider of HIV care (ie, Southern Alberta Clinic [SAC]).

METHODS

Study Population

All individuals who had their first confirmed positive HIV test in the Alberta Health Services, Calgary Zone between January 1, 2006 and January 1, 2013 were included in the study. The Calgary Zone has a catchment population of approximately 1.2 million people in 2013. All individuals living with HIV are referred to the SAC in Calgary, Alberta, which provides free access to all HIV services, including ART, under universal healthcare. The nearest alternative HIV care clinics are located 180 miles (300 km) away. Individuals were followed from the date of their first positive HIV test date to the time they moved out of the area, were lost to follow-up ([LTFU] defined as no clinic

contact, laboratory tests, or ART use for 12 or more months), died, or November 30, 2013, the study end date. We included only individuals newly diagnosed in our local area and excluded patients who were diagnosed elsewhere and had transferred their care to us. Locally diagnosed patients who left the area or were LTFU and then returned were retained for analysis.

Approach

In Alberta, HIV became a notifiable disease in 1998 [26]. All deaths and causes of death are reportable to Alberta Health. Through linking the Calgary area HIV clinical care database (SAC) with the Calgary area Public Health information, we determined the position in the cascade of care of all individuals with a positive test. We determined whether they (1) were diagnosed but never linked to HIV care, (2) were referred for HIV care but never attended, (3) attended their first visit and registration but never attended subsequently, (4) were retained in care, (5) were retained in care but did not receive ART (ie, remained ART naive), (6) were retained in care but were not virally suppressed, and (7) were retained in care and were virally suppressed.

We defined treatment cascade categories that align with but are modified from those presented by Nosyk et al [3]. The term “HIV infected” refers to all individuals living with HIV regardless of whether they are aware of their status. This category includes all newly diagnosed HIV infections and those estimated by the Public Health Agency of Canada (PHAC) [27] to be HIV infected who are unaware of their status and likely living in Calgary. We used the high estimate of 25% for unknown HIV cases. Therefore, we include both the known and estimated HIV population in the overall analysis. The “HIV diagnosed” individuals are those with a confirmed HIV-positive test. Individuals “linked to HIV care” are those who are referred to SAC after testing, usually by their testing physician. On receipt of the referral a patient record is initiated at SAC. Individuals “retained in care” refers to patients who have had at least 2 regular clinic visits within 12 months of their HIV diagnosis and had HIV-specific laboratory tests (either a CD4 cell count and/or plasma viral load test) performed. Program objectives at SAC are to have all newly diagnosed patients attend, within 1 week of their referral, an introductory visit with the SAC nursing team and social workers before their first physician appointment, which should follow within 2 weeks. The objectives of the introductory visit are to establish patient rapport, provide HIV education and social support, answer and address immediate concerns (such as disclosure, prevention, and financial and disability entitlements), and obtain baseline blood work. Patients attending the introductory visit but no further appointments are considered linked to care but not retained in care. We categorized retained patients as ART-naive or ART experienced and monitor whether ART has been interrupted for more than 3 months for any reason. Viral suppression is defined as

maintaining an undetectable plasma viral load for 12 consecutive months before either moving, being LTFU, death, or as of November 30, 2013.

Date and cause of death was verified through the Alberta Death Registry or from secondary sources if the individual had died after moving outside the province. The cause of death was classified using the CoDe system [28]. Mortality rates are calculated per 100 person-years followed (/100 person years) by dividing the number of deaths by the total number of years followed (ie, from HIV diagnosis date to date of death, moved, LTFU, or November 30, 2013 multiplied by 100. We then assessed where in the cascade of care patients died.

We used simple descriptive statistics including population totals, mean, standard deviation, and, where appropriate, χ^2 analysis with $P < .05$ at the level of significance. The use of this administrative data is approved by the University of Calgary Conjoint Medical Committee on Medical Bioethics.

RESULTS

Cascade of Care

Between January 1, 2006 and January 1, 2013, there were 543 newly confirmed HIV diagnoses in individuals residing in the Calgary area. Sixty-five (12.0%) of these HIV diagnoses were made in hospitalized patients. Using high PHAC estimates [29], we determined that there were an additional 137 (25%) individuals in the region who are unaware of their HIV infection, giving a total estimated number of 680 new HIV cases.

Forty-three newly diagnosed individuals (7.9%) known to Public Health were never referred to SAC for assessment. The remaining 500 (92.1%) of known cases were referred to SAC (Table 1).

Eighty-eight (17.6%) of the 500 individuals linked to HIV care were not subsequently retained in care; 67 did not attend their introductory visit in the study time frame; and 21 attended only the introductory visit but did not proceed to the phlebotomy laboratory (approximately 20 feet away from SAC on same floor of the building) to have baseline blood work (plasma HIV viral load or CD4 count) completed nor did they attend a subsequent regular clinic visit with a physician.

Four hundred twelve individuals (82.2% of all referrals) were retained in care (60.6% of all estimated HIV infections within the region). The median time of follow-up for patients retained in care throughout the study period was 58 months (interquartile [IQR], 43–76); for patients who moved, 17 (IQR, 7–33) months; for patients LTFU, 13 (IQR, 8–36) months; and for patients who died, 8 (IQR, 2–30) months. The majority (87.6%) of retained patients received ART at some point, with 12.4% remaining ART naive due to maintaining high CD4 counts, undetectable viremia, or the patient's personal choice. Overall, 12.8% of retained patients had at least 1 LTFU episode (ie, >12 months without clinic contact) during the study period.

Antiretroviral therapy naive patients were more likely to have ever been LTFU compared with ART-experienced patients (31.5% vs 9.4%; $P < .001$) (data not shown). Of all patients retained in care, 76.1% (ie, 313 of 411) had achieved viral suppression by study's end. For all locally diagnosed HIV cases, and for all estimated cases during the study period, the level of viral suppression was 57.6% and 46.0%, respectively.

Deaths Within the Cascade of Care

A total of 36 deaths occurred in HIV patients who had been diagnosed within the Calgary area between January 1, 2006 and January 1, 2013. The overall mortality rate was 1.50/100 person-years followed (Table 1). The distribution of deaths and causes of death were unequally spread through the cascade of care. Figure 1 illustrates the cascade of care in standard form, the proportion of individuals not accessing care, and proportion and location of deaths within the cascade depicted below the x-axis.

Only 1 death occurred in the 43 diagnosed and 137 estimated undiagnosed cases that were not linked to HIV care in any form. This patient was diagnosed with HIV posthumously. The remaining 35 deaths occurred in individuals who had at one time been linked to care albeit not necessarily retained in care or on ART.

Twenty of the 35 deaths (57%) occurred in individuals who were linked or referred to care but had no regular clinic visits. These individuals either did not receive ART or in some cases did not complete baseline laboratory testing for CD4 count or plasma viral load. The mortality rate was 6.93/100 person-years. In 70% of these 20 deaths ($n = 14$), the cause of death was AIDS. Six deaths occurred in patients who were hospitalized at the time of their HIV diagnosis. Overall, 12% ($n = 65$) of all new HIV diagnoses occurred shortly before, during, or shortly after (ie, <7 days) a hospitalization; nearly 1 in 10 of these patients died. Five of the 14 deaths occurring outside of a hospitalization were in patients who had attended an introductory visit for care (ie, HIV program nurse/social worker contact) but failed to return for a first physician appointment.

For patients retained in HIV care, the overall mortality rate was 0.79/100 person-years. Only 1 patient died while ART naive (0.42/100 person years); this patient had declined ART. All of the patients who died were being actively followed at the time of their death. The mortality rate was 0.85/100 person-years for all ART-experienced patients. Five of the 14 (36%) ART-experienced patients who died were not actively receiving ART; 4 of these 5 had elected to discontinue ART. Patients with detectable HIV viremia had a higher death rate, 2.49/100 person years, compared with patients achieving viral suppression at 0.28/100 person years. Patients who died while retained in care were more likely to have had a lower mean initial CD4 count ($63/\text{mm}^3$ vs $290/\text{mm}^3$), a higher rate of AIDS comorbidity at HIV diagnosis (46% vs 14%), have intravenous

Table 1. All Newly Diagnosed Cases of HIV Reported in Southern Alberta Between January 1, 2006 and January 1, 2013. All Known Deaths Are Reported Occurring Between January 1, 2006 and November 30, 2013 for All Causes of Death

	N	Deaths (%)	Rate per 100/Person Years followed	Total Pt yrs Followed
HIV Infected				
Estimated number of all HIV cases in region ^a	680 (100%)	36 (100%)	*	
All confirmed ^b new HIV diagnoses	543 (79.8%)	36	1.50/100	2398
Linked to HIV Care^c				
Estimated number of all HIV cases in region	500 (73.5%)	35 (97%)		
All confirmed new HIV diagnoses	500 (92.1%)	35	1.61/100	2183
Not Linked to Care				
Estimated number of all HIV cases in region ^d	180 (26.3%)	1 (3%)		
All confirmed new HIV diagnoses	43 (7.9%)	1	0.46/100	215
Linked to HIV Care but not retained^e				
All confirmed new HIV diagnoses	88 (16.2%)	20 (55%)	6.93/100	289
Retained in care^f				
Estimated number of all HIV cases in region	412 (60.4%)	15 (42%)		
All confirmed new HIV diagnoses	412 (75.9%)	15	0.79/100	1895
Retained in care and ARV naive ^g	50 (12.1%)	1 (3%)	0.42/100	240
Retained in care and ARV experienced	361 (87.6%)	14 (39%)	0.85/100	1655
Retained in care and not virally suppressed ^h	99 (24.1%)	11 (30%)	2.49/100	442
Retained in care and virally suppressed	313 (75.9%)	4 (11%)	0.28/100	1449
Number of all estimated and known HIV cases virally suppressedⁱ				
	313 (46.0%)			

Abbreviations: ARV, antiretroviral; HIV, human immunodeficiency virus.

*Rate not shown because it is not possible to determine follow-up times in undiagnosed individuals.

^a Based on known cases + (known cases x .25) = total estimated cases.

^b Confirmed by Calgary area Public Health.

^c Individuals linked to HIV care are those who are referred to SAC (Southern Alberta Clinic) directly from contact with Public Health after a positive test, or directly from a physician, or from admission to hospital, or from another source.

^d Based on unknown estimated HIV cases + known confirmed cases.

^e Individuals linked to care (ie, SAC) but no regular clinic visits with HIV physicians. Note, at SAC, new patients attend a preassessment visit with the nursing team, pharmacists, and social workers before their first regular clinic appointment with the HIV care physicians. If a patient attended the preassessment appointment but no subsequent regular clinic visits, they were considered linked to care but not retained in care.

^f Individuals retained in care refer to patients who have had at least 2 regular clinic visits and had diagnostic laboratory tests (ie, CD4 cell count and/or plasma viral load test) performed.

^g Patients are categorized as ARV-naive or ARV-experienced.

^h Virologically suppressed is defined as maintaining an undetectable plasma viral load for 12 consecutive months before either moving, being lost to follow up, death, or November 30, 2013 (end of study).

ⁱ Based on 313 of 680.

drug use as their most likely risk factor (26.6% vs 7.3%), and were older at diagnosis (median = 47 vs 37 years) compared with survivors (small sample size precludes statistical significance). For 8 of the 15 deaths (53%), the cause of death was AIDS.

DISCUSSION

Using the cascade of care definitions, we evaluated the distribution of HIV infection and deaths within the HIV public health and care programs provided by a single administrative jurisdiction in a defined geographic location with universal access to free healthcare. Although 92% of diagnosed cases of HIV

infection were linked to HIV care, only 58% of confirmed cases achieved viral suppression; this proportion decreases to 46% if the estimated 25% of undiagnosed HIV infections are included. Although this percentage is slightly higher than reported elsewhere [1–3], it is still disappointing and likely lower than needed to significantly impact local HIV transmission. One quarter of newly diagnosed individuals were not retained in regular care, and they did not receive the benefits of freely available ART. Of the patients accessing and retained in care, 88% used ART and 76% achieved viral suppression for >12 consecutive months with a decreased risk for HIV-related mortality. Patients who receive regular care are more than 8 times less likely to die than those linked to care but not retained. Reflecting

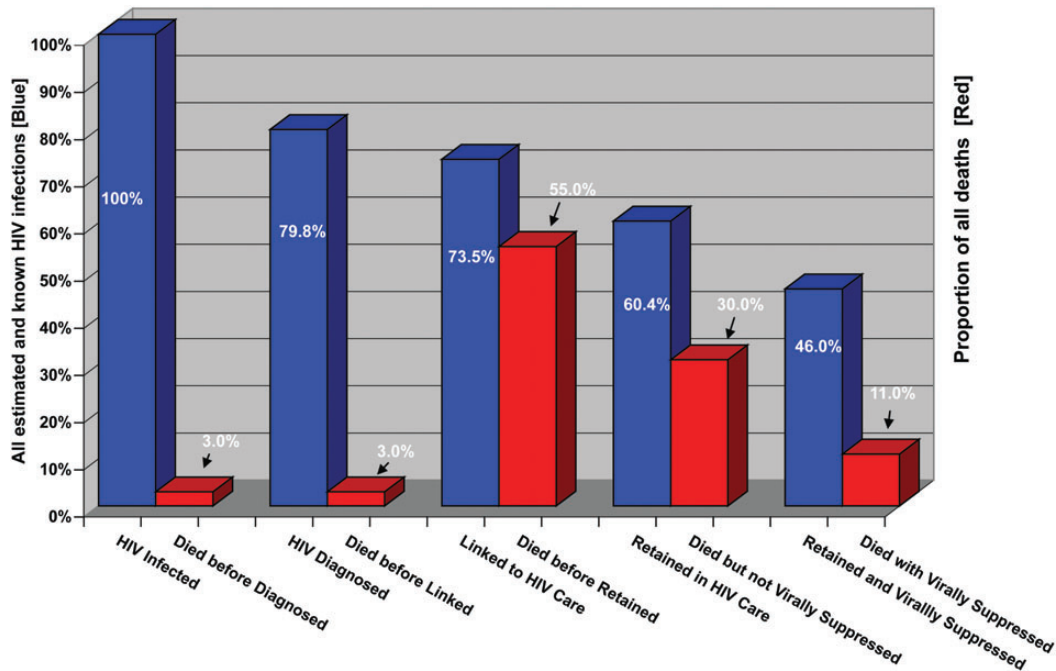


Figure 1. Cascade of care for all new human immunodeficiency virus (HIV) infections (estimated and known cases = 680) in the Alberta Health Services, Calgary region from January 1, 2006 to January 1, 2013. Placement and proportions of all-cause deaths (N = 36) are shown in red.

others' reports [22–25], we also found that a significant proportion of deaths occurred after an initial linkage but before full engagement to care.

The 1 patient diagnosed posthumously is intriguing. We have not found other studies in the modern ART era that report patients who get diagnosed after death, although we suspect that this case is not unique and it should remind us of the pool of infected patients who remain undiagnosed in their lifetime. Other individuals received a positive HIV test but either declined referral or were not referred to HIV care. Failure of linkage to HIV care may have resulted if the test was anonymous and the individual failed to return to receive the results, or if they did not return to the ordering physician and Public Health could not contact them, or if they ignored the results, or if the individuals tested were transient to the area and could not be found.

Over half of the deaths occurred in individuals who had been linked to HIV care but were never fully retained. The reasons for failure to successfully engage and be retained in care is multifactorial. Bertolli et al [29] notes that fear, inability to cope with their HIV diagnosis, feeling healthy, and/or structural factors all contribute to the lack of connectiveness to HIV care. The high rate of death before accessing HIV-specific care suggests that “seek and treat” [30, 31] alone may not be enough if HIV care linkage and retention is not addressed adequately. The 16% of patients linked but not retained in care accounted for 57% of all deaths. We were surprised to find that nearly 1 in 4 linked

patients who died had limited their clinic contact to the introductory visit. The issue of patients who are linked, albeit even transiently, to HIV care who do not then fully engage needs to be addressed.

Our results suggest that the use of a cascade of care, without considering deaths, may not fully represent the complexity of the epidemic or reflect the importance of the ultimate and most important clinical endpoint (death) if it is being used as a comprehensive metric of program performance. Individuals with HIV infection who die without accessing or being retained in care are often missed in large-scale studies examining mortality rates and causes of death in HIV populations [13–16]. Cohort studies mostly include patients only after they have accessed care. As such, individuals not retained in care are missed and hence deaths that occur before care is accessed are also not included, and these deaths are often overlooked. Our study has shown that a significant number of deaths do occur at this early point in the cascade of care.

Once patients are retained in care and use ART, mortality decreases significantly. Retained patients who died in this cohort were diagnosed with much lower initial CD4 counts, indicating late presentation of their HIV disease. Patients not achieving or maintaining viral suppression were also much more likely to die, a finding that has long been discussed by others [17].

Our study, although comprehensive, does have limitations. Our site is unique in that there is a single care provider that can monitor patient movements into and out of the area with

more precision than in other sites; however, individuals with HIV infection can move through the area without contacting or utilizing HIV care and thus would not be included in our study. The number of undiagnosed HIV infections according to PHAC, although based on the best available information nationally, remains an estimate. In our linked but not retained category, we include those patients who were diagnosed and died with HIV infection in hospital before regular clinic care could be started. Optimal placement of these patients in the cascade is unclear, but we placed them arbitrarily in this category because the other surviving patients diagnosed with HIV in hospital were classified as retained in HIV care. Rather than using cross-sectional data, we followed patients over 8 years, and as such the proportions in our cascade categories may not be directly comparable with other studies. The relative merits of using cumulative or cross-sectional data for cascade analysis are currently under discussion.

Our study also differs from other studies describing the cascade of care in that it only focuses on newly diagnosed local patients and does not include patients moving into the area who were previously diagnosed and received HIV care outside of the region. We included only HIV patients newly diagnosed in our area to minimize any bias in analyzing access to care and retention issues. In most cascade of care studies, it is unclear whether in-migrated (and previously treated) patients are included or indeed should be included. We excluded them to avoid any bias from mixing engagement to care and transfer of care issues that may be different.

CONCLUSIONS

Increasing the proportion of individuals living with HIV infection who are virally suppressed is the goal of any HIV treatment program. Patients retained in care and accessing ART on a regular basis have significantly better outcomes and lower rates of mortality than patients delaying or not accessing care. Our study highlights the association with mortality with unsuccessful linking and engagement to care. The reasons patients fail to link to care are likely multifactorial. Ongoing efforts should be intensified to not only seek individuals who may be infected, but to ensure that they link up with and maintain HIV care to ensure optimal outcomes and reduce disease transmission.

Notes

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