

Why Are People on HIV Treatment Still Dying?

Dr. Elvin Geng Explores True Mortality in Zambia

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Across provinces in the southern African country of Zambia, it can take hours to reach the closest healthcare facility – not a trip that can be done easily or frequently. Early in the AIDS epidemic, clinics were the only place where one could get tested for HIV and ultimately get treatment for HIV.

In recent years, access to HIV testing and education programs in developing countries has expanded into community health fairs, churches and faith groups, and even bars and shops – and a positive test result can link an individual to care in a facility closest to them. An emphasis on prevention has reduced transmission in many parts of the world – undoubtedly an achievement to be celebrated. But how much do we know about HIV-positive individuals years down the line – how long they live on treatment, for example, or what trends emerge in terms of opportunistic and comorbid diseases?

It's a question that had been troubling UCSF physician-researcher Dr. Elvin Geng [1] for years.

In trying to determine meaningful metrics, he asks, "Does achieving success in controlling HIV mean no more infections? Or no more deaths?"

Though both important, he says, "on the surface, these look like similar questions. But in reality, they're really quite different."

Resource-limited settings have always posed challenges for practitioners hoping to track the progress and health status of those on antiretroviral treatment (ART) – getting an accurate picture of those who are dying despite having been on ART is no exception.

This is nowhere more evident than in Southern Africa. Despite HIV deaths decreasing by 50 percent in the last fifteen years, it's not always clear what's working in terms of service delivery and what's not. Implementation of care, it's increasingly clear, can fundamentally alter one's quality and length of life when living with the virus.

?Getting accurate information regarding true mortality is exceptionally difficult because what is seen as ?routine? monitoring doesn?t actually capture deaths,? explains Geng, who sees patients in San Francisco at the General Hospital and executes his global research primarily in Zambia and Kenya.

The idea of getting a more precise picture of the number of people actually dying while on treatment gained traction a few years ago during Geng?s time as a fellow under the tutelage of Dr. Jeff Martin [2], while working with a group of epidemiologists and clinicians involved in the NIH-funded consortium known as the International Epidemiology Databases to Evaluate AIDS [3] (IeDEA) ? a network dedicated to pooling data to generate large sets serving to highlight and address priority research questions in HIV.

?There has always been a lot of interest in the effectiveness of global HIV treatment ? but people were primarily interested in how many people you get on drugs, or how many people adhere to the treatment. There was little interest in whether people were surviving on treatment,? says Geng. Data was pouring into IeDEA on the former two measurements, but not much was emerging on the latter.



In reality, whether or not people are dying once taking what is understood to be lifesaving treatment is probably the most important question of all. So why don?t we know more?

There are a few reasons. It?s easy to count people currently on and accessing treatment, but there isn?t a reasonable way of systematically ascertaining death data, largely due to infrastructure and stability issues in developing regions. Patients that switch clinics (not a small number, as many engage in migrant work, move to be closer to family or for cheaper housing, or relocate to regions with more promising economic developments) are easily lost given that there?s no easy, reliable way for clinics to communicate with one another.

This loss to follow-up (LTF) prompts investigators to query whether patients have dropped out of care at their initial clinic because they had difficulty getting there, were encumbered with family care, had insurmountable mental and emotional distress, or because they engaged in care elsewhere. All cause unique issues, and either going off treatment full-stop or experiencing a break in care can lead to deadly consequences.

Geng decided to explore the data more thoroughly with colleagues from Georgetown University, led by Dr. Charles Holmes, and the Center for Infectious Disease Research in Zambia, known as CIDRZ [4], with results published earlier this year in PLOS Medicine [5]. A true partnership project known as Better Information for Health in Zambia ("BetterInfo"), Geng mined the relationships he's fostered after years of working in the region with local clinicians and investigators.

Undertaking a multi-stage sampling-based survey across four provinces and 64 government-operated clinic sites, Geng and colleagues also worked with the Zambian Ministry of Health in examining data from more than 160,000 patients over a two-year period. They were interested in a few specific questions: the magnitude of deaths of those who were taking ART; when these deaths occurred; which groups on ART are at highest risk of death; and whether these factors differ by region, facility, or other variables. The only qualifiers were adults over the age of 18 who had made a clinic visit in the last two years. All clinics were government supported and CIDRZ operated.

The multi-stage sampling was important, Geng notes, because of its generalizability ? while some studies have explored LTF in smaller regions and cohorts, they have been approached more as case studies, not representative population-based studies allowing for deeper epidemiological exploration, with findings that can be applied across regions.

The team leveraged the electronic medical record systems in the four most populous provinces of Zambia to enumerate their cohort, then performed extensive chart reviews to find those who appeared to be lost to follow up ? and then tried to find as many as they could in the surrounding regions.

?About 30,000 of the 160,000 people were lost to follow-up,? Geng admits. ?We looked for 3,500, and we found 75 percent of them over the course of 6 months.?

This process, known as ?tracing?, is more of a social activity than a geographical one ? essentially, you find the people who know how to find the rest, Geng explains. Community leaders aligned with clinics know the best ways to find specific individuals, whether it's through their landlord, their pastor, their teacher, or another link in the community.

After finding these individuals or their families, the team looked for specific answers ? if they hadn't passed away shortly after their last visit, had they gone to other clinics? If they had, how much longer were they on treatment a second time before experiencing other health problems, or switching clinics again? Were there other gaps in care before they passed, and for how long?

For those with gaps in care, there was a relatively big delay between leaving their original clinic and starting at their second one ? the better part of a year, in fact. This is problematic, as this delay ? or the in and out pattern of treatment that many patients go through ? prompts viremia, spikes in viral load, and drug resistance. These lead to long-term complications for

the individual and their community. (Spikes in viral load increase the likelihood of transmission between partners, and drug resistance makes HIV harder to control around the world.)

The findings were illuminating, and almost inadvertently showed just how difficult accurate mortality information is to harness. According to some clinics' records, it looked like less than a 2 percent death rate over 2 years; Geng and team discovered it was more like 8 to 9 percent overall.

The death rate was low among those reliably on treatment for a long time, but the proportion of total deaths is still far too high – those on treatment for over a year represented 60 percent of deaths, with a rate of 1 to 2 percent a year. It wasn't until getting to about 8 years on treatment when that rate began to decrease – which was surprising.



‘I figured there would be very little dying one to two years out,’ Geng admits.

Additionally – and distressingly – about half of deaths among those newly starting ART occurred relatively soon after a clinic visit – suggesting a missed opportunity in understanding concurrent health and risk factors in patients’ lives.

Also interesting was the discovery that CD4 count at initiation of treatment – often considered a harbinger of an HIV-positive individual’s quality and length of life – had little association with early mortality. What does have an association is the nature of the way their care is delivered.

‘This is a clarion call for implementation,’ Geng emphasizes. ‘The biology matters – but it doesn’t matter that much. There is a lot of other stuff going on.’

These findings provide a wealth of new research opportunities in Zambia for Geng and colleagues.

Next, "we want to focus our improvement efforts on clinics that represent a small proportion of the population, but a lot of deaths," he says. The significant variability among clinics across regions points to this need. Mortality rates from site to site ranged from less than 1 death per 100 person-years to up to 13.4 deaths per 100 person years.

There were a handful of clinics that represented a high number of overall deaths among patients "and there are practical improvement methods in implementation that can be targeted particularly to their specific needs, ultimately reducing deaths.

"We now have information related to particular barriers to care across individual clinics, and we can use it in a quality improvement way "tailored uniquely to clinic users" responses about avoiding care due to stigma in their community, difficulty in getting transportation to the clinics to access medication, trouble communicating with a provider, things like that," he says. These targeted approaches tend to have a more impactful outcome, as they cater directly to the concerns and needs of the population.

He's also expanding geographically, and is now working with UCSF researcher Dr. George Rutherford [6] to answer similar questions in Kenya.

What lessons from this first project might he bring east?

"Implementation matters," Geng underscores. "It's not just getting the drugs. How you reach people, how you treat them, how you cater to their needs "it's really essential."

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Photos are of clinics in the Magoye province, courtesy of Monica Roy, MD [8].

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