The performance of verbal autopsy tools for capturing HIV/AIDS-related mortality in sub-Saharan Africa

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1. ***Background***

HIV is a persistent public health problem which claimed nearly a million deaths in 2017 (WHO fact sheet). In light of the Joint United Nations Programmes on HIV/AIDS (UNAIDS) aim to reduce AIDS-related by a half by 2020 (UNAIDS 2016), it is imperative to accurately and directly measure HIV-related mortality. However, high HIV-prevalence settings commonly suffer from poor coverage of civil registration systems (D'Ambruso et al 2017), a lack of medically certified causes of death, and social stigma surrounding HIV, making it tough to truly understand its associated mortality burden (Chambers et al 2015; Karat et al 2018).

Verbal Autopsies (VA) are a common and relatively cheap alternative to medical certification of causes of death (CoDs) in low-income settings (Araya et al 2012; de Savigny 2017; D'Ambruso et al 2017; Karat et al 2018). VAs make use of a standardized questionnaire on the signs and symptoms that the deceased experienced in the illness episode preceding their death and are typically administered with a relative of the deceased (Nichols et al 2018). CoD ascertainment on the basis of a VA interview are commonly done using physician reviews or computer algorithms, including InSilicoVA, InterVA and Tariff (Araya et al 2012; Byass et al 2012; McCormick et al 2016).

The administering of ART in high HIV-prevalence settings has been associated with improvements in HIV/AIDS-related mortality (Karat et al 2018; Reniers et al 2014). However, it remains unclear whether the effectiveness of VA tools in correctly capturing HIV/AIDS-associated mortality varies across settings with varying levels of HIV-prevalence. It is also unknown whether the tools differ in effectiveness as the burden of HIV/AIDS-related mortality shifts into older ages and can be more difficult to distinguish from other CoDs.

Using data from three Health and Demographic Surveillance Sites (HDSS) in Southern and Eastern Africa, where the HIV status of a large fraction of the population is known, we assess the ability of VAs to capture HIV/AIDS-related mortality. More specifically, we examine whether the performance of VAs decline with reductions in HIV-prevalence and an older age-distribution of deaths. We present our results for each sex separately and using different VA interpretation tools. We quantify the performance of VAs in terms of their sensitivity and specificity.

2. ***Data***

We use data from three members of the Network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA Network): Kisesa (Tanzania), Karonga (Malawi) and uMkhanyakude (South Africa). These datasets are assembled from different sources, including demographic surveillance repeated population-based HIV serosurveys, and VAs. This data is described elsewhere in greater detail (Reniers et al 2016, Slaymaker et al 2017). All our analyses pertain to adults aged between 15 and 100 years old. Karonga and Kisesa are regarded as low HIV-prevalence sites, with an average prevalence among 15-100-year olds of 11.4% and 6.3% among women respectively, and 8.4% and 4.8% among men, respectively in the 2006-17 period. Conversely,

uMkhanyakude is regarded as a high prevalence site with a prevalence of 41.4% and 23.4% among women and men, respectively.

3. Methods

We define the sensitivity of VA tools as the fraction of the life-years lost (YLL) between ages 15 and 100 attributed to an HIV indicative diagnosis, where the YLL is the difference in adult life expectancy (LE) of known HIV-negatives and the population as a whole. In other words, we use the HIV-negative population to represent a counterfactual case of the general population in the absence of HIV-associated mortality. Hereafter we also refer to this quantity as the adult LE deficit at age 15 (LE15 deficit). We decompose differences in LE15 by CoD using the Arriaga method (Arriaga 1984), and later calculate how much of the LE15 deficit is attributed to each CoD. Following Byass et al (2013), we report results for four HIV/AIDS indicative causes of death: HIV/AIDS, Pulmonary Tuberculosis (TB), Severe Malnutrition, and Acute Respiratory infection (ARI).

We define the specificity as the fraction of YLL among known HIV-negatives that is correctly attributed to a cause that is not indicative of HIV/AIDS. In this case, we use the 2016 Japanese age-pattern of mortality from the Human Mortality Database as the counterfactual (Wilmoth and Shkolnikov 2010). As in the GBD studies, we compute the YLL to a particular CoD as the sum of Japanese life expectancies at the age of death for each of the HIV-negative individuals who reportedly died from any of the causes under consideration.

In the preliminary results reported below, we ascertained CoDs using the InSilicoVA tool (Clark et al 2015). After obtaining the CoD distribution for each individual, we assigned a single CoD to each individual corresponding to the cause with the highest probability. We subsequently group the CoDs into the following categories: HIV/AIDS, TB, Severe Malnutrition, and Acute Respiratory infection, Other communicable diseases, External causes, Maternal causes, and Other Non-Communicable Diseases.

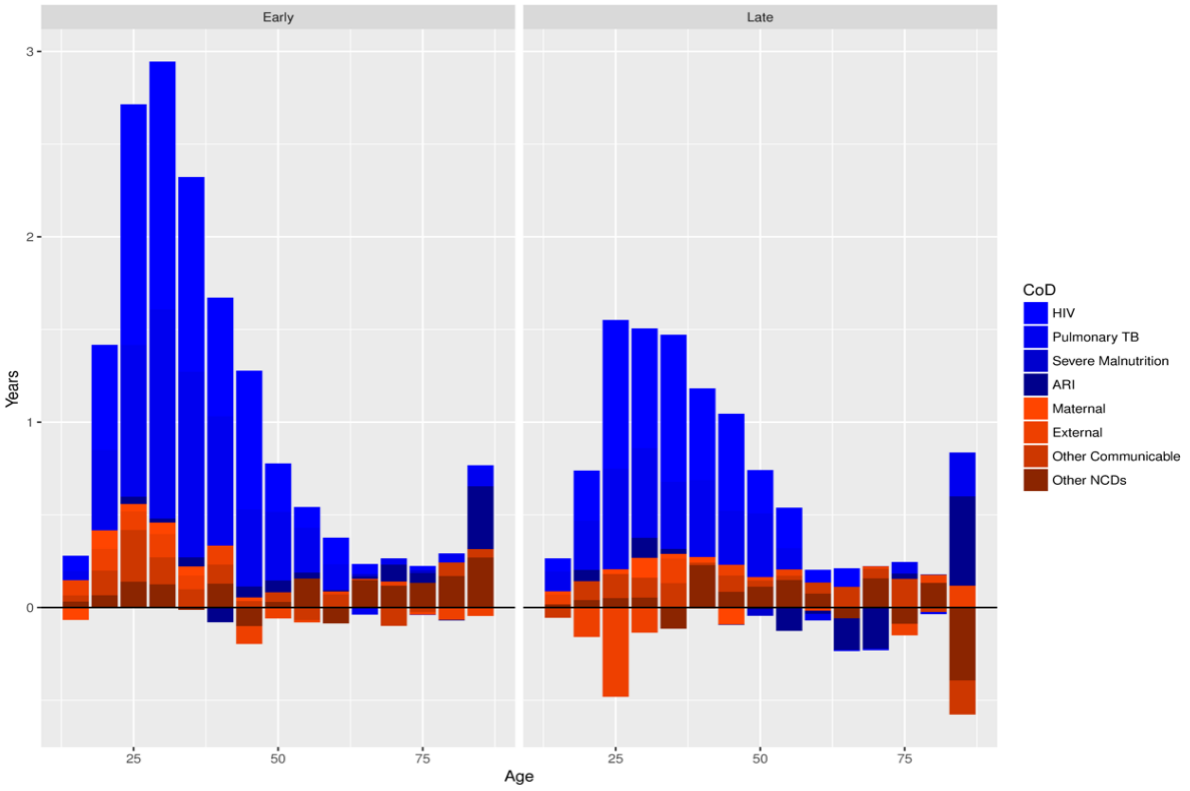
We smoothed mortality curves for men and women in each of the three sites using the 'MortalitySmooth' R package developed by Camarda (2012) which smooths Poisson mortality and exposure counts using p-splines. Fitted mortality rates were subsequently used in period lifetables to derive estimates of LE15.

In this abstract, we only report on VA outputs that have been obtained using the InSilicoVA, but in the full paper we also report on CoDs that were ascertained with Physician Review, InterVA, and possibly Tariff.

4. Results

In Figure 1, we show results of the age-cause decomposition of the LE15 deficit for women in uMkhanyakude for two periods following the introduction of ART: Early (2006-10) and Late (2011-2016). Each bar in these plots represents the per capita YLL due to mortality in that particular age group, which is further decomposed by cause. Negative values in this figure indicate that the mortality rates from a particular cause are higher among HIV negatives than in the population as a whole, but their contribution is usually small and could be due to stochastic variation. From Figure 1, we observe that that (i) the LE15 deficit declined over time (the sum of the YLL is lower in the most recent period), (ii) the age profile of the LE15 deficit became older, and (iii) that most of the LE15 deficit is attributed to HIV/AIDS-indicative causes of death (i.e, portion of the bars that are blue).

Figure 1: Age-cause decomposition of the LE15 deficit among women in uMkhanyakude, (early: 2006-10; late: 2011-2016).



We repeated the age-cause decomposition illustrated in Figure 1 for each of the study sites and computed the proportion of the LE deficit is attributed by the VA to each of the causes under consideration. Results are separately reported for two broad age groups (15-49 and 50+). In contrast to Figure 1, the results are reported for the two periods combined, and the sensitivity is reported cumulatively, meaning that the first column represents the proportion of the LE15 deficit that is attributed by the VA tool to HIV/AIDS, the second column is the proportion of the LE deficit that is attributed to HIV/AIDS or Pulmonary TB, and so forth. Analogously, the values for the specificity of the VA tools are reported cumulatively. As expected, the sensitivity of the VA tools generally increases, and specificity generally declines, as more CoDs are added (in the current set of results there are a few exceptions due the negative contributions of some causes to the LE deficit; an issue that we will address by the time of the conference).

Preliminary analyses indicate that the specificity of the VA tools for identifying HIV/AIDS mortality is relatively high. A couple of exceptions aside, the specificity is above 90% for HIV/AIDS alone, and ranges between 66% and 96% for HIV/AIDS and Pulmonary TB combined. When Severe malnutrition and ARI are also considered as HIV/AIDS indicative CoDs, the specificity usually remains above 80%, but declines to 59% in the case for older men in uMkhanyakude. We do not observe any systematic differences in the specificity by sex, but values are generally higher for older compared to younger adults. One exception to this observation pertains to the specificity of older men in uMkhanyakude after adding Pulmonary TB as an HIV/AIDS indicative diagnosis. This can be explained by the relatively high mortality from TB among older HIV-negative men (Reniers et al 2017). Including it as an HIV/AIDS indicative diagnosis would thus result in the erroneous attribution of deaths to HIV/AIDS and lower the specificity of the VA tool.

The estimated sensitivity values are generally lower than specificity and characterized by greater heterogeneity. First, the sensitivity of the HIV/AIDS indicative diagnose is generally lower for older compared to younger adults, which suggests that HIV/AIDS related deaths presented with a more diverse symptom pattern in older adults that is more difficult to interpret by means of a VA. Second, the sensitivity is higher in uMkhanyakude than in the two other study sites. Incidentally, uMkhanyakude also has much higher HIV-prevalence than Karonga and Kisesa, suggesting that VA tools perform better at picking up HIV/AIDS-related mortality in high-prevalence settings. However, this comes at a loss in specificity (cf. men in uMkhanyakude). Third, the sensitivity of the

HIV/AIDS indicative CoDs appears to be higher for women than for men. This is particularly the case for younger women, suggesting that it may be related sex differences the in age-distribution of HIV infections and HIV/AIDS related mortality. Again, uMkhanyakude is an exception.

Table 1a: Cumulative Sensitivity and Specificity of VA tools by study site and age (Women)

	HIV/AIDS		***+Pulmonary TB***		***+ severe malnutrition***		***+ Acute respiratory infections***	
	Sens	*Spec*	*Sens*	*Spec*	*Sens*	*Spec*	*Sens*	*Spec*
Karonga								
15-49	0.573	1.000	0.709	0.941	0.715	0.941	0.706	0.793
50+	0.219	1.000	0.242	0.949	0.263	0.949	0.355	0.913
Kisesa								
15-49	0.644	0.785	0.611	0.700	0.611	0.700	0.639	0.700
50+	0.262	0.926	0.333	0.859	0.353	0.830	0.448	0.800
uMkhanyakude								
15-49	0.475	0.795	0.850	0.679	0.850	0.679	0.865	0.634
50+	0.366	0.979	0.701	0.876	0.702	0.868	0.818	0.716

Table 1b: Cumulative Sensitivity and Specificity of VA tools by study site and age (Men)

	HIV/AIDS		***+Pulmonary TB***		***+ severe malnutrition***		***+ Acute respiratory infections***	
	Sens	*Spec*	*Sens*	*Spec*	*Sens*	*Spec*	*Sens*	*Spec*
Karonga								
15-49	0.490	0.994	0.651	0.963	0.651	0.963	0.745	0.919
50+	0.430	1.000	0.516	0.950	0.514	0.950	0.723	0.888
Kisesa								
15-49	0.208	0.908	0.342	0.863	0.342	0.863	0.342	0.863
50+	0.225	0.954	0.113	0.893	0.211	0.893	0.248	0.872
uMkhanyakude								
15-49	0.296	1.000	0.935	0.817	0.946	0.817	0.963	0.817
50+	0.407	0.975	0.986	0.662	0.982	0.643	0.973	0.585

5. Concluding remarks

This is one of the first studies to quantify the sensitivity and specificity of VAs for identifying HIV/AIDS mortality using population-based data from sub-Saharan Africa. These preliminary analyses highlight considerable variability in the sensitivity, and to a lesser extent specificity of VAs, and suggest that the performance of VAs depends on the age, sex and HIV prevalence in the study population. The case of uMkhanyakude further suggests that high mortality from TB (irrespective of HIV status) further complicates the identification of HIV/AIDS deaths on the basis of a VA interview.

6. Additional work ahead of the conference

Ahead of the conference, we intend to refine the estimation procedures, add data from other study sites that are member of the ALPHA Network of population-based HIV surveillance sites (http://alpha.lshtm.ac.uk), and also report on results that make use of alternative VA interpretation methods (Physician Review, InterVA, and Tariff). Preliminary analysis using InterVA (not shown) show similar results to those presented in this abstract.

References

1. World Health Organization 2018, Fact Sheet – HIV/AIDS, Media Centre [online] Available at: http://www.who.int/news-room/fact-sheets/detail/hiv-aids [Accessed 13 Sep. 2018].
2. World Health Organization, Joint United Nations Programme on HIV/ AIDS (UNAIDS). Guidelines for HIV mortality measurement. 2014. https://www.ncbi.nlm.nih.gov/books/NBK236997/pdf/Bookshelf_ NBK236997.pdf (accessed 15 Mar 2018).
3. de Savigny D, Riley I, Chandramohan D, *et al*. Integrating community-based verbal autopsy into civil registration and vital statistics (CRVS): system-level considerations. *Glob Health Action* 2017;10:1272882.
4. Karat, A.S., Maraba, N., Tlali, M., Charalambous, S., Chihota, V.N., Churchyard, G.J., Fielding, K.L., Hanifa, Y., Johnson, S., McCarthy, K.M. and Kahn, K., 2018. Performance of verbal autopsy methods in estimating HIV-associated mortality among adults in South Africa. *BMJ global health*, *3*(4), p.e000833.
5. Araya, T., Tensou, B., Davey, G. and Berhane, Y., 2012. Accuracy of physicians in diagnosing HIV and AIDS-related death in the adult population of Addis Ababa, Ethiopia. *World Journal of AIDS*, *2*, pp.89-96
6. Chambers, L.A., Rueda, S., Baker, D.N., Wilson, M.G., Deutsch, R., Raeifar, E. and Rourke, S.B., 2015. Stigma, HIV and health: a qualitative synthesis. *BMC Public Health*, *15*(1), p.848.
7. D'Ambruoso, L., Boerma, T., Byass, P., Fottrell, E., Herbst, K., Källander, K. and Mullan, Z., 2017. The case for verbal autopsy in health systems strengthening. *The Lancet Global Health*, *5*(1), pp.e20-e21.
8. McCormick, T.H., Li, Z.R., Calvert, C., Crampin, A.C., Kahn, K. and Clark, S.J., 2016. Probabilistic cause-of-death assignment using verbal autopsies. *Journal of the American Statistical Association*, *111*(515), pp.1036-1049.
9. Flaxman, A.D., Joseph, J.C., Murray, C.J., Riley, I.D. and Lopez, A.D., 2018. Performance of InSilicoVA for assigning causes of death to verbal autopsies: multisite validation study using clinical diagnostic gold standards. *BMC medicine*, *16*(1), p.56.
10. Byass, P., Chandramohan, D., Clark, S.J., D'ambruoso, L., Fottrell, E., Graham, W.J., Herbst, A.J., Hodgson, A., Hounton, S., Kahn, K. and Krishnan, A., 2012. Strengthening standardised interpretation of verbal autopsy data: the new InterVA-4 tool. *Global health action*, *5*(1), p.19281
11. Reniers, G., Slaymaker, E., Nakiyingi-Miiro, J., Nyamukapa, C., Crampin, A.C., Herbst, K., Urassa, M., Otieno, F., Gregson, S., Sewe, M. and Michael, D., 2014. Mortality trends in the era of antiretroviral therapy: evidence from the Network for Analysing Longitudinal Population based HIV/AIDS data on Africa (ALPHA). *AIDS (London, England)*, *28*(4), p.S533.
12. Reniers, G., Wamukoya, M., Urassa, M., Nyaguara, A., Nakiyingi-Miiro, J., Lutalo, T., Hosegood, V., Gregson, S., Gómez-Olivé, X., Geubbels, E. and Crampin, A.C., 2016. Data resource profile: network for analysing longitudinal population-based HIV/AIDS data on Africa (ALPHA Network). *International journal of epidemiology*, *45*(1), pp.83-93
13. Slaymaker, E., McLean, E., Wringe, A., Calvert, C., Marston, M., Reniers, G., Kabudula, C.W., Crampin, A., Price, A., Michael, D. and Urassa, M., 2017. The Network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA): Data on mortality, by HIV status and stage on the HIV care continuum, among the general population in seven longitudinal studies between 1989 and 2014. *Gates open research*, *1*.
14. Arriaga, E.E., 1984. Measuring and explaining the change in life expectancies. Demography, 21(1), pp.83-96.
15. Clark, S.J., McCormick, T., Li, Z. and Wakefield, J., 2015. InSilicoVA: a method to automate cause of death assignment for verbal autopsy. *arXiv preprint arXiv:1504.02129*.
16. Camarda, C.G., 2012. MortalitySmooth: An R package for smoothing Poisson counts with P-splines. *Journal of Statistical Software*, *50*(1), pp.1-24
17. Byass, P., Calvert, C., Miiro-Nakiyingi, J., Lutalo, T., Michael, D., Crampin, A., Gregson, S., Takaruza, A., Robertson, L., Herbst, K. and Todd, J., 2013. InterVA-4 as a public health tool for measuring HIV/AIDS mortality: a validation study from five African countries. *Global health action*, *6*(1), p.22448.
18. Wilmoth, J.R. and Shkolnikov, V., 2010. Human mortality database. *University of California*.
19. Reniers, G., Blom, S., Lieber, J., Herbst, A.J., Calvert, C., Bor, J., Barnighausen, T., Zaba, B., Li, Z.R., Clark, S.J. and Grant, A.D., 2017. Tuberculosis mortality and the male survival deficit in rural South Africa: An observational community cohort study. *PloS one*, *12*(10), p.e0185692.