Evaluating the performance of the InterVA Model for determining AIDS mortality in the Adult Population of Addis Ababa.

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Abstract

Background Verbal Autopsy (VA) is a method for determining cause of death based on post mortem interview with caregivers. It is a useful tool in areas where routine death registration is inadequate. Most commonly, causes of death are assigned by physicians who review completed VAs. Algorithms like the InterVA model are alternative ways to assign cause of death from VA. The objective of this paper is to evaluate the performance of InterVA model using reference standard.

Methods Surveillance of hospital admissions and outpatient visits from the TB/HIV clinic was initiated in Zewditu Memorial Hospital. A VA interview was conducted for those died in and out of the hospital. The InterVA model is used to interpret the VA interviews to arrive at probable causes of death.

Results One hundred ninety three VAs were interpreted using the model and the probability of the most likely cause of death is 82%. The proportion of AIDS death determined by the reference standard is 56% while that of the InterVA is 61%. The sensitivity and specificity of AIDS death are 0.84 and 0.76 respectively. Likewise, sensitivity and specificity values of TB/AIDS death are 0.92 and 0.78, respectively.

Conclusion The analysis of VA using InterVA model to estimate AIDS mortality produces promising results when compared to the reference standard.

Key Word: Verbal autopsy, InterVA, cause specific mortality traction, TB/AIDS.

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INTRODUCTION

Mortality statistics are important tools in the era of HIV/AIDS to evaluate the effectiveness of Anti Retroviral Therapy (ART) programmes. In developing countries estimating the distribution of cause of death is difficult due to the low coverage of vital registration [1-5]. Verbal Autopsy (VA) is an alternative way of estimating cause specific mortality based on post mortem interview with next of a kin or other caregivers. It is increasingly used in places where medical certification of cause of death is insufficient [6, 7].

Interpretation of VA largely relies on either expert assessment of the VA interviews by physicians, or other application of predetermined algorithms. Physician review has been shown to be a reliable tool for VA interpretation but is subject to standardization, change of expertise and large volume of work [8-10]. Algorithms permit automation of the coding process and hence have the advantage of low cost to be used on a large scale but need to be validated against external data sets [11]. The InterVA model is one of those algorithms and has been evaluated in Vietnam and Ethiopia [12, 13].

The objective of this paper is twofold. First, we evaluate the performance of the InterVA model against a reference standard constructed from hospital records including patients' HIV serostatus. Validation studies typically compare assigned cause of death from VAs to hospital records. However, hospital records may be a poor reference standard for AIDS in communities where the deceased and their caregivers are often unaware of HIV status, a social stigma surrounds AIDS and hospital utilization is limited. HIV serostaus of the deceased individual is, however often unavailable, and a reliable tool, with known sensitivity and specificity, would allow the estimation of the level of AIDS mortality in populations with unknown serostatus [14]. Second, we use the InterVA model to estimate the Cause Specific Mortality Fraction (CSMF) of TB/AIDS.

STUDY AREA AND POPULATION

The population size of Addis Ababa is approximately 2.7 million in 1999 [15]. The first AIDS cases were diagnosed in 1986 [16]. In 2005, the prevalence of HIV/AIDS in the country is 1.4% with urban and rural values of 5.5% and 0.7%, respectively. For Addis Ababa the prevalence is 4.7%, with great disparity between men (3%) and women (6%) [17]. Estimates based on extrapolations from antenatal clinic (ANC) data are considerably higher [18].

METHODS

Data

We use two data sources (Figure 1). The first is based on nine-month surveillance in a large governmental hospital in the inner city of Addis Ababa, Zewditu Memorial Hospital. The surveillance covered the TB-HIV clinic (ambulatory patients only), the medical emergency, internal medicine, gynecology, surgical, and pediatric wards. For each patient, a ward nurse collected basic background characteristics as well as the admission and discharge diagnosis. A Determine rapid HIV1-2 test was carried out on the blood sample and the VCT nurse carried out post-test counseling. Capillus™ HIV-1/HIV-2 confirmatory tests were performed on positive samples, and if the outcomes of both tests were discrepant, a Uni-Gold™ HIV test was done as a tie breaker. Tests were offered free of charge. For patients that died during or subsequent to their visit, we tried to retrieve the patient card. In total, 1,650 patients were registered, and an HIV test was administered for 1,332 of them.

The second data source is a set of verbal autopsy interviews that were carried for (1) patients that died in the hospital under surveillance, and (2) for patients who died elsewhere, but whose hospital record matched with that from an ongoing surveillance of burials. The burial surveillance was initiated in February 2001 at all known cemeteries in the capital and described elsewhere [19, 20]. Via the match of burial and hospital records, we retrieved patients who visited the hospital during the course of their terminal illness, but did not die there. Verbal autopsy interviews were conducted two to nine months ($\bar{x} = 4.7$) after the death by a pair of community health workers who received a one-week training. Figure 1 shows the data collection process and the study protocol.

Reference Standard

Data from the hospital surveillance were used to construct the reference standard. Cause of death is defined based on the admission diagnosis, HIV test result and patient cards. Patient cards were retrieved only for 73 records (Annex I).

InterVA

InterVA accepts a range of signs and symptoms as indicators processes them in a mathematical model based on Baye's theorem, and produces likely cause(s) of death with their associated probabilities [21]. Bayes' theorem defines the conditional probability of a cause (C) denoted as $P(C|I)$, given the presence of a particular indicator (I). The indicators I_1, I_2, …., I_n collected from VAs lead to a set of causes of death C_1, C_2, …,C_m. Thus, for a particular case, the probability of C_k is initially the value found among deaths in general, which is the cause specific mortality fraction at the population level [13, 22].

Both pre-coded and open-ended questions were used to describe the whole range of information about the circumstances of death, including background characteristics, details of illness (signs and symptoms) leading to death, previous medical history, etc. The prevalence of malaria and HIV/AIDS were entered as low and high, respectively. The model presents its findings as probable cause(s) of death. Up to three likely causes with their likelihood may be given for a particular case [21]. Likely causes of death were used to generate dichotomous variables of AIDS and TB/AIDS death. An AIDS death is defined as one where any of the likely cause of death refers to HIV/AIDS related death for all levels of likelihood.

Validation Study

Likely causes of death produced by the model are compared with the reference standard. Sensitivity and specificity figures were calculated for different cut-off points of likelihood. Tuberculosis and AIDS are combined since these two diseases often occur in the same subject and have many symptoms in common, so it is unlikely that the VA can discriminate between them [8].

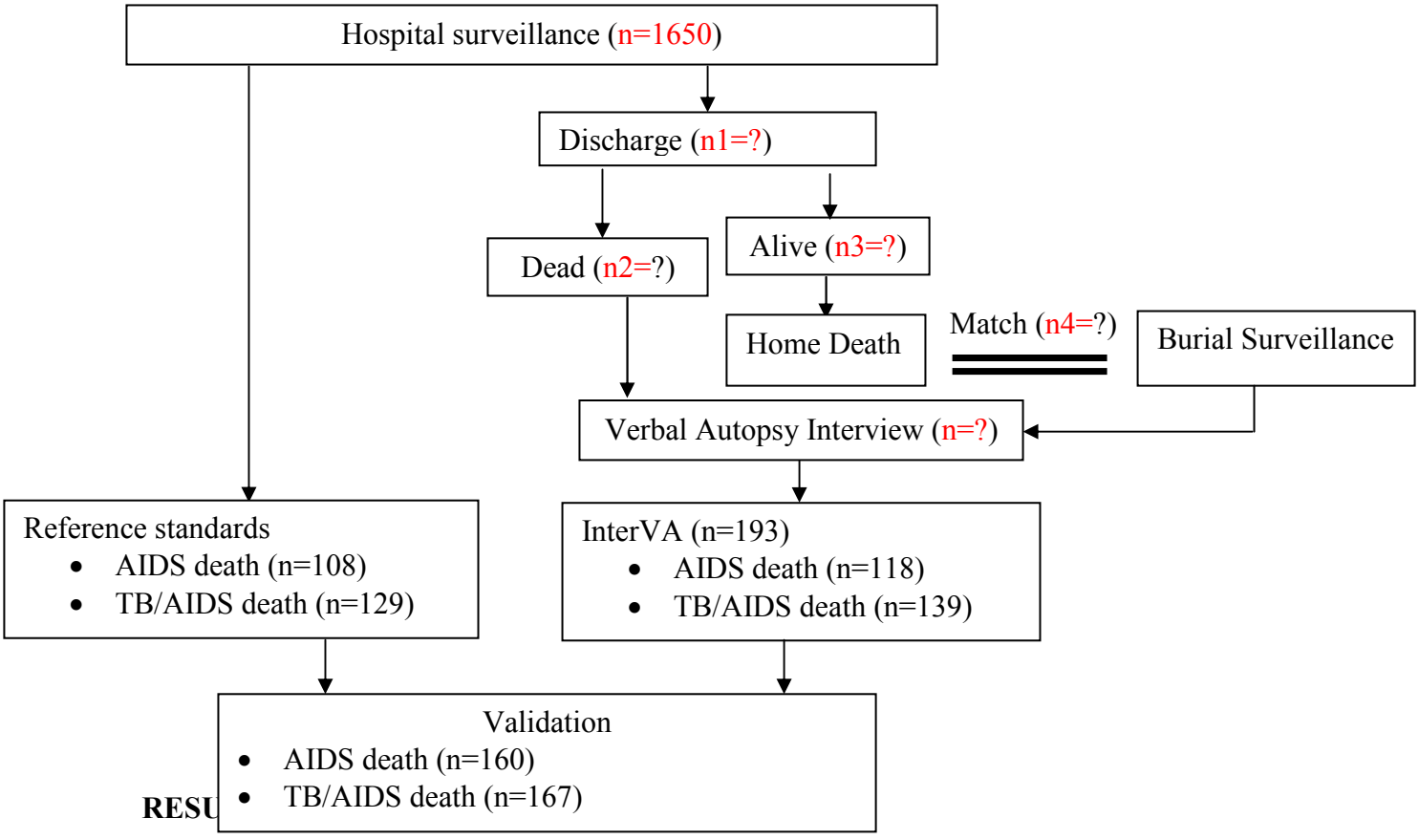


Fig 1. Flow chart showing the study protocol and data collection

RESU

One hundred ninety three VA's were conducted for that died at the hospital and elsewhere but ales with a sex ratio of 0.95. Eighty eight percent of the observations are on the age interval 15-59. Of those who were

approached for counseling, 82.4% of the respondents had tested for HIV with a prevalence of 63.5%.

In the reference standard 56% of the records had been identified as AIDS death and 13.5% (n=26) were not classified as AIDS/non-AIDS death due to lack of required information such as HIV test result. Similarly, 66.8% were identified as TB/AIDS death. Nearly 10% (n=19) of the records were not classified as TB/AIDS or non-TB/AIDS death (Table 1).

Table 1. Cause specific mortality fraction of AIDS, TB/AIDS death in the reference standard

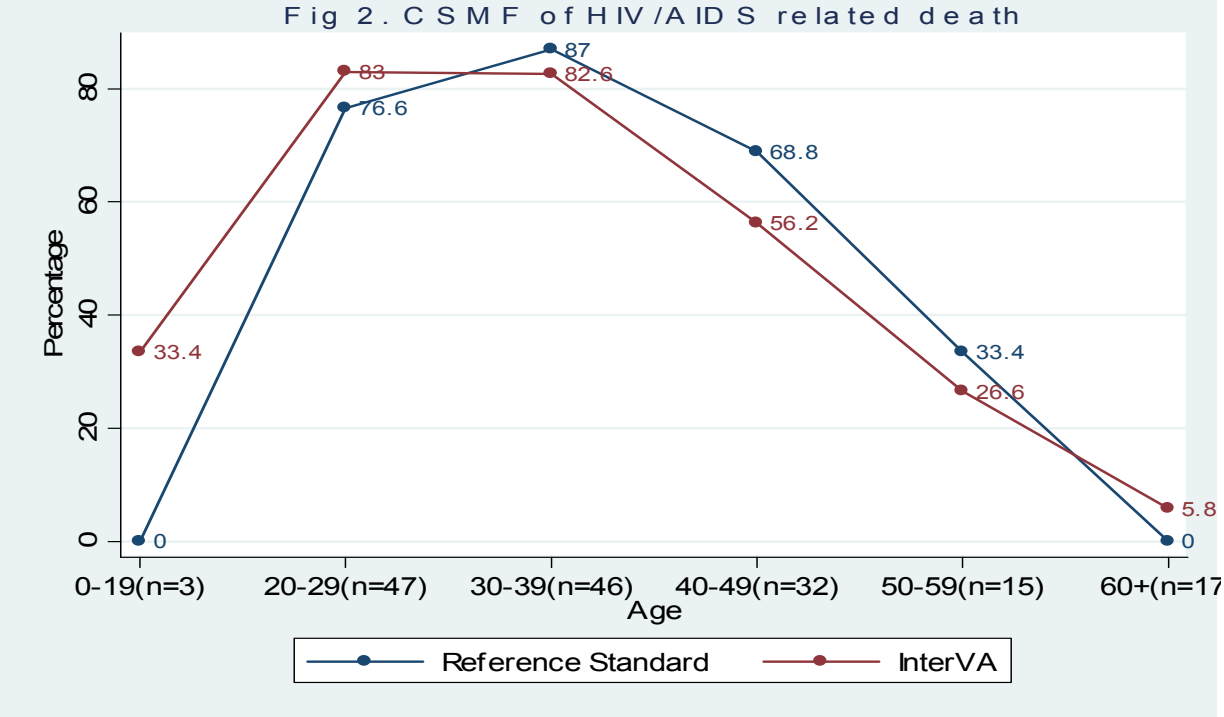
Cause of Death	Female		Male		Total	
	n	%	n	%	n	%
AIDS Death	54	54.55	54	57.45	108	55.96
TB/AIDS Death	63	63.64	66	70.21	129	66.84

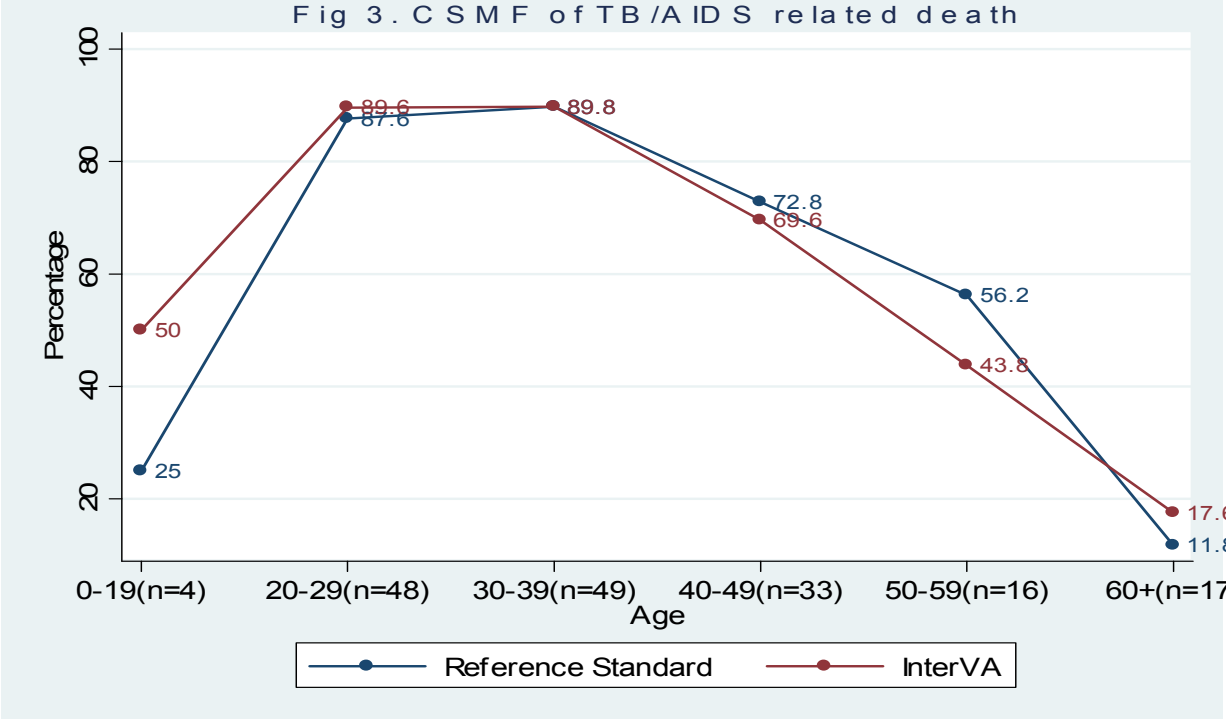
The model assigned a CSMF for HIV/AIDS and TB/AIDS death to be 61.1% and 72%, respectively. The mean likelihood of most likely cause of death is 82%. Based on the most likely cause of death HIV/AIDS is a major cause (54.9%) followed by liver disease (15%) and pulmonary tuberculosis (14.5%). Twenty-seven observations had a second likely cause of death with a probability of 40.4%. None of the observations had a third likely cause of death (Table 2).

Table 2. The distribution of the major cause of deaths using the InterVA model.

		n	%	Mean probability
Most likely causes of Death	HIV/AIDS	106	54.9	86.2
	Liver disease	29	15.0	84.0
	Tuberculosis (pulmonary)	28	14.5	80.8
	Others	30	15.5	66.5
Second Likely causes of Death	HIV/AIDS	12	44.4	41.0
	Liver disease	3	11.1	34.3
	Tuberculosis (pulmonary)	6	22.2	44.0
	Others	6	22.2	38.5

The InterVA and the reference standard gave identical classification in 81% of the records as AIDS/non-AIDS death. A similar comparison for TB/AIDS death gives a value of 88%. There is a similarity between the CSMF of the model and the true values in diagnosing HIV/AIDS as a cause of death by age as shown in figures 2 and 3.





The sensitivity and specificity values of the model in estimating AIDS mortality are 0.84 and 0.76, respectively. On the second classification of deaths as TB/AIDS, the sensitivity and specificity values elevate to 0.92 and 0.78, respectively (Table 3). There is a remarkable increase in the sensitivity results with the level of the most and second likelihoods while specificity is roughly steady for upper thresholds. Receiver Operating Characteristics (ROC) curve is sketched to visualize the performance of the model for different levels of the

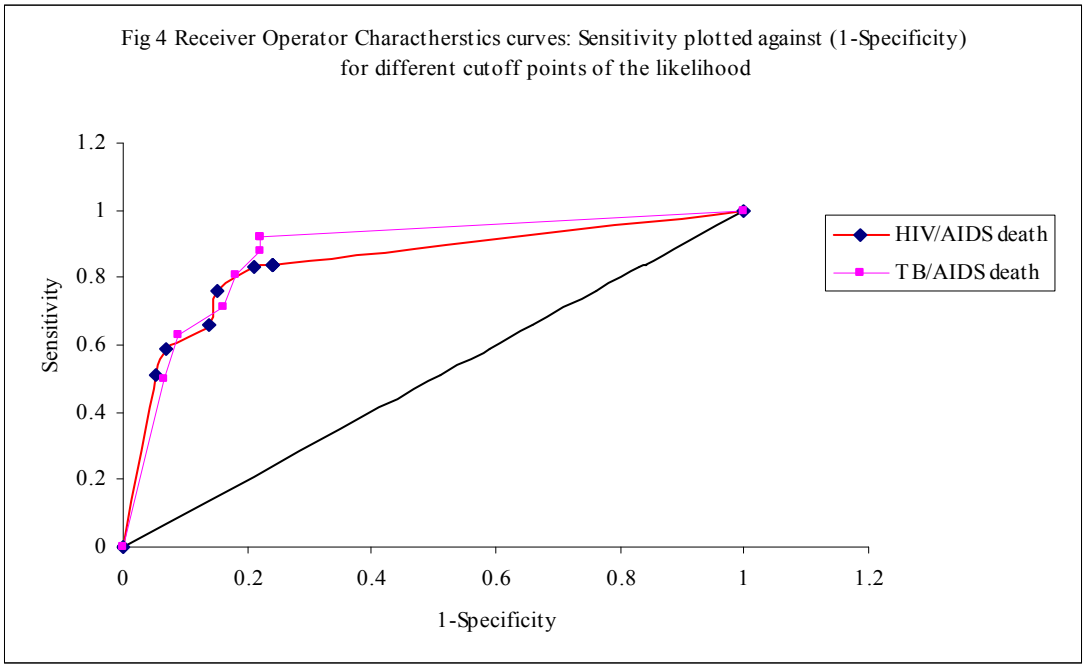
likelihoods. The optimum ROC area is obtained if probability of likely causes of death is above 90 and 80 for AIDS death and TB/AIDS death, respectively. (Fig 4, Annex II).

Table 3. Sensitivity, specificity values and area under ROC curve.

	Sensitivity	Specificity	ROC area
AIDS Death	0.84	0.76	0.7995
	(0.76,0.91) *	(0.63,0.86) *	(0.733,0.866)*
TB/AIDS Death	0.92	0.78	0.8479
	(0.85,0.96)*	(0.63,0.89)*	(0.782,0.914)*

* 95% Confidence Interval

PPV = Positive Predictive value, NPV= Negative Predictive Value



Discussion

Different validation studies for the VA method have been done for deaths in children [23-26] and adults [9, 10] suggesting that the VA method is an important tool for diagnosing causes of death, predominantly in developing countries. Studies in Tanzania [27] and in Ethiopia [12] have shown the robustness of the VA method in identifying cause of death using lay interviews. There are many factors that influence the validity of a VA tool [11]. The absence and lack of parallelism between variables in the VA questionnaire and indicators of the model is one factor reducing the accuracy of the model to be more realistic with that of the gold standard. Interviewers comment regarding the truthfulness and cooperativeness of the respondent, though not build in the model improves the model's performance. In a society with poor knowledge of symptoms of certain disease relevant information are explained more in local terms and parallel comparison with the

close-ended indicators of the model may be challenging. Hence the use of the open ended questions in the questionnaire as an additional input improves accuracy of the model. Culture specific factors such as stigma and discrimination, also reduced the performance of the model. The relatively small sample size of the study also contributes to underestimating performance and also did not allow the estimation of CSMF and validity of other causes of death. The performance of the model has been assessed in subjects who were treated at hospital and the model may perform differently to those subjects who were not treated at hospital.

VA results are not based on clinical or laboratory measures, and are subject to a relatively high degree of misclassification error resulting in a profound effect on the accuracy of the VA estimate. The difference between the true proportion of death and the VA estimate from specific cause demonstrates both the magnitude and direction of the estimates [6, 28]. The algebraic value of the difference of the VA estimate from the reference standard indicates that the VA underestimates the CSMF of AIDS death (diff = 0.0125). The VA correctly estimates the CSMF of TB/AIDS death (diff = 0). Moreover, VA estimates of CSMF can be inaccurate if the sensitivity and specificity of the VA are less than one. One way of overcoming this problem is by adjusting the VA estimate of CSMF using the sensitivity and specificity of the VA tool. The method of adjusting the CSMF for the effect of misclassification error is described elsewhere [28]. The adjusted CSMF of the VA estimate is equal with the true CSMF for AIDS and TB/AIDS death.

The use of VA for assessing causes of death in a population is relatively a new phenomenon. Verbal Autopsy is potentially an alternative technique to examine cause of death due to specific cause in countries where vital registration is either weak or non-existent. InterVA model is most suitable for determining TB/AIDS mortality and useful tool to measure the impact of ART on mortality. The analysis of VA based on probabilistic model produces promising results primarily for those settings where physician review is not feasible or too costly.

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Annex I

Table for defining the reference standard using admission diagnosis (ICD-10), HIV status and transcribing patient cards.

HIV test result	AIDS Death		
	Yes	No	Not Classified
Positive	A09,A10-A19,A41,B02, B20, B24,B37,B58,B59,C53, G03, G04,I95,J98,J18,K60,K75, R40,R50,R57,R69	V01-V09, W65-W74, W75-84,X00-X09, X40-X49 O95-O97	B50,B54,E14,I10,I15 K29,K30,U99,C50
	(96)	(0)	(5)
Negative		Any Diagnosis	
	(0)	(58)	(0)
Not Available	B58,B59,B20,B24,C53 Patient card (PCP,RVI, hydropneumothorax, Oral Thrush, oesophagal candiasis, hypotension, toxoplasmosis, etc…)	A35, E16 I10, K27,K31, K35,K38, K72, N81, O05 and died shortly (with in seven days) patient card (HPN stroke)	A09, A15,A16,A19,A35, A41, A68 B50,B54,C50, D39,D64, E14,E16, G03, I10,I15, I95,J18, K27, K29 K30,K31,K38,K72, K76,N73,N81,O05 , R50, R57, R62,R69,T14
	(12)	(1)	(21)

*Numbers in the bracket are frequencies that fall in the classification.

Annex II

Probability of likely cause of death	AIDS Death			TB/AIDS Death		
	Sensitivity	Specificity	ROC Area	Sensitivity	Specificity	ROC Area
>10	0.51	0.95	0.7995	0.51	0.93	0.8479
>20	0.59	0.93	0.7995	0.63	0.91	0.8479
>30	0.66	0.86	0.7995	0.71	0.84	0.8479
>40	0.77	0.84	0.7927	0.81	0.82	0.8400
>50	0.83	0.79	0.7991	0.88	0.78	0.8362
>60	0.84	0.76	0.8111	0.92	0.78	0.8440
>70	0.84	0.76	0.7995	0.92	0.78	0.8365
>80	0.84	0.76	0.8338	0.92	0.78	0.8677
>90	0.84	0.76	0.8488	0.92	0.78	0.8577

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