Estimating cumulative mortality of HIV-1 infected patients at 2 years after starting ART in sub-Saharan Africa using methods for modelling missing data to account for loss to follow up: the IeDEA Prognostic Model

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Background In sub-Saharan Africa the International epidemiological Databases to Evaluate AIDS (IeDEA) initiative facilitates the collection of prospective data on patients starting ART. Monitoring and evaluating scale up programs delivering ART in Africa depend on obtaining accurate data on outcomes. Previous analyses from ART-LINC indicated that observed 1-year survival was worse in cohorts that had active follow up compared with those that had passive follow up (Lancet 2006 367 817-24), a result almost certainly due to inadequate ascertainment of deaths. Current work on prognostic models for patients starting ART in sub-Saharan Africa has used imputation of missing outcomes in patients lost to follow up (ltfup). Here we explore some of the methodological issues associated with estimating 2 year mortality rates in this context.

Methods We used data from 4 cohorts from South Africa, Côte d'Ivoire and Malawi with active follow-up and good ascertainment of death. Eligible patients were aged >15 years, started triple ART and had a baseline CD4 count recorded. We calculated the Kaplan-Meier (KM) survival estimate at 2 years after starting ART using the observed data and censoring those ltfup. Kernel density estimation was used to compare the distribution of CD4 counts in those who were and were not ltfup. We then used multiple imputation to account for missing data in prognostic factors and outcomes using the STATA ice command that uses chained regression equations. The interval censoring option was used to impute survival times in those ltfup with the lower limit of the survival time set to the date of the last known contact with the patient and the upper limit set to missing (mathematically infinity). Those ltfup with an imputed survival time less than 2 years were considered dead whilst those with a survival time greater than 2 years had their times censored to 2 years in

subsequent modelling. The revised KM survival estimate at 2 years was calculated by averaging the results from 5 imputed datasets.

Results 10210 patients experienced 903 (8.8%) deaths. The KM estimate of cumulative mortality at 2 years was 10.1% assuming data missing completely at random (MCAR) and 11.7% conditioning on covariates (ie assuming data missing at random (MAR)). The table shows results overall and for each cohort. The cohort with the smallest observed proportion of deaths at 2 years (D), had the highest ltfup, the lowest cumulative mortality based on MCAR and the highest cumulative mortality based on MAR assumptions.

Discussion The KM estimate of cumulative mortality takes into account short follow up due to patients starting ART less than 2 years before database close and also censoring due to loss to follow up, but assumes that data is MCAR. This is unlikely to be the case in cohorts with poorer ascertainment of deaths and imputing outcome conditional on covariates measured at start of ART (MAR) is likely to result in a less biased estimate of mortality. Only linking with death registries could determine whether ltfup is informative after conditioning on covariates (ie data missing not at random (MNAR)).

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Cohort	No (%) patients	Pyears follow up	No. (%) lost to fup	No. (%) deaths within 2 years	KM estimate of 2 year cumulative mortality	
					Observed	MI
A	2262 (22)	2923	395 (17)	199 (8.8)	9.6 (8.4,11.0)	11.2 (9.8,12.8)
B	1806 (18)	2030	358 (20)	148 (8.2)	9.8 (8.3,11.5)	11.3 (9.5,13.1)
C	3277 (32)	4683	349 (11)	333 (10.2)	10.9 (9.8, 12.1)	11.5 (10.3,12.7)
D	2865 (28)	2491	690 (24)	223 (7.8)	9.2 (8.0,10.6)	12.9 (10.9,14.9)
All	10210 (100)	12127	1792 (18)	903 (8.8)	10.1 (9.4,10.7)	11.7 (10.9,12.5)