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Predicting mortality within 1 year of ART initiation in children and adolescents living with HIV in sub-Saharan Africa: a retrospective observational cohort study

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AKa, BL, YM, EC, HLK, and AMM conceived and designed the study. AKa, SD, AS, TS, LK, PD, PA, EK, PE, AMu, and AMs contributed to data curation and investigation of the study question. AKa, AS, and HLK directly accessed and verified the underlying data. AKa, BL, NM, SN, YM, EC, HLK, AS, AKe, LT, LM, and AMM contributed to data analysis and interpretation. AKa and AMM drafted the manuscript. All authors contributed to revising and editing the final manuscript. All authors had full access to the data in the study and read and approved the final version of the manuscript.

See **Online** for appendix

Declaration of interests

We declare no competing interests.

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Summary

Background—Differentiated service delivery (DSD) for children and adolescents living with HIV can improve targeted resource use. We derived a mortality prediction score to guide clinical decision making for children and adolescents living with HIV.

Methods—Data for this retrospective observational cohort study were evaluated for all children and adolescents living with HIV and initiating antiretroviral therapy (ART); aged 0–19 years; and enrolled at Baylor clinics in Eswatini, Malawi, Lesotho, Tanzania, and Uganda between 2005 and 2020. Data for clinical prediction, including anthropometric values, physical examination, ART, WHO stage, and laboratory tests were captured at ART initiation. Backward stepwise variable selection and logistic regression were performed to develop predictive models for mortality within 1 year of ART initiation. Probabilities of mortality were generated, compared with true outcomes, internally validated, and evaluated against WHO advanced HIV criteria.

Findings—The study population included 16 958 children and adolescents living with HIV and initiated on ART between May 18, 2005, and Dec 18, 2020. Predictive variables for the most accurate model included: age, CD4 percentage, white blood cell count, haemoglobin concentration, platelet count, and BMI Z score as continuous variables, and WHO clinical stage and oedema, abnormal muscle tone and respiratory distress on examination as categorical variables. The area under the curve (AUC) of the predictive model was 0·851 (95% CI 0·839–0·863) in the training set and 0·822 (0·800–0·845) in the test set, compared with 0·606 (0·595–0·617) for the WHO advanced HIV criteria ($p<0·0001$).

Interpretation—This study evaluated a large, multinational population to derive a mortality prediction tool for children and adolescents living with HIV. The model more accurately predicted clinical outcomes than the WHO advanced HIV criteria and has the potential to improve DSD for children and adolescents living with HIV in high-burden settings.

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Introduction

Access to HIV care for children has improved over the past decade through decentralisation of care and task shifting enabled by a public health approach. This improvement has resulted

in large reductions in mortality for children and adolescents living with HIV through the early introduction of antiretroviral therapy (ART).[1] Differentiated service delivery (DSD) strategies for children with ART, such as multi-month prescribing, have been developed and are often contingent on viral suppression to reduce the effect of HIV on the lives of children and adolescents.[2,3] However, nearly 100 000 children continue to die annually in sub-Saharan Africa due to HIV or AIDS.[4] Tools are needed that support direction of health-care resources to children at the highest risk to make the greatest impact in reducing mortality.

A public health approach to HIV care should be augmented by tools that more accurately predict outcomes in children and adolescents who are enrolling in care.[5] Adult studies have identified phenotypes to help stratify the risk of death following ART initiation.[6] Risk factors for mortality in children and adolescents living with HIV have been identified, such as immunosuppression, clinical stage, malnutrition, and opportunistic infections.[7–10] Attempts to derive mortality prediction tools in children have been limited by derivation from children in high-resource settings,[11,12] single-centre data,[13], or limited accuracy.[14] Mortality prediction tools in HIV-positive adults have shown promise, but they have also been derived and validated among cohorts in high-resource settings.[15,16] Currently, all children diagnosed with HIV younger than 5 years meet the WHO criteria for advanced HIV, which limits the ability to risk stratify management within this population based on this commonly used criteria.[17] To address this gap, we have derived a generalisable mortality prediction tool for children and adolescents living with HIV initiating ART in sub-Saharan Africa.

Methods

Study design and participants

This retrospective observational cohort study was aligned with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[18] The primary objective of the study was to develop a risk score for mortality within the first year following ART initiation.

The study population included children and adolescents living with HIV initiating ART at six centres of excellence (COE) within the Baylor College of Medicine clinical network of Indigenous foundations across five countries: Eswatini, Lesotho, Malawi, Tanzania (Mbeya and Mwanza), and Uganda. To reduce bias, all ART-naive children and adolescents living with HIV enrolled and cared for at the COEs aged 0–19 years at ART initiation were included in the analysis.

All clinical investigation supporting the data handling, analysis, and reporting of these findings was conducted according to the principles of the Declaration of Helsinki. Approval was obtained from the national ethical bodies in each country and the Baylor College of Medicine Institutional Review Board with details provided in the appendix (p 4).

Procedures

Patient data were extracted and analysed from the electronic medical record (EMR) as previously reported.[19,20] In brief, the database allows extraction of longitudinal patient-level data (abstracted by SD and site monitoring and evaluation officers in March, 2021). The period of analysis differed among the COEs based on the year of clinic opening and timing of the introduction of the EMR (2005–11; appendix p 5), and included clients initiated on antiretroviral therapy up to 2020. Children and adolescents living with HIV who were retained in care and who had fewer than 365 days of post-initiation follow-up were excluded from the analysis. Covariates thought to be potential predictors were identified a priori, and included sex, age, BMI Z score (defined by WHO growth charts), WHO stage, CD4 percentage, physical examination findings, and laboratory findings. These data were isolated from a clinical visit within 90 days of ART initiation. If there were multiple values within this period, the value closest to ART initiation was selected.

Outcomes

Mortality was the primary outcome. However, considering the high risk of death among children and adolescents living with HIV who are lost to follow-up (LTFU)[21] and the known effect of age at ART initiation on the risk of mortality, planned sensitivity analyses were performed assuming those who were LTFU died within 1 year, and the model was applied in an age-stratified population of children and adolescents living with HIV aged 0–4 years and 0–11 years. Post-hoc analyses for mortality within 3–6 months of ART initiation, early ART initiation (initiated between 2005 and 2011), and late ART initiation (initiated between 2012 and 2020), were performed.

Statistical analysis

The dataset was compiled and evaluated for missingness. Covariates with less than 40% missingness were considered for inclusion. Data were divided at a 7:3 ratio between the training and test sets, evenly matched by the outcome of interest. Imputation of missing data was performed using multiple imputation by chained equations (MICE) with random forests (R package mice, v3.16.0). Variables included in the imputation are reported in the appendix (p 3). Imputation with random forests handles mixed data types and remains accurate for variables with up to 75% missingness within large datasets.[22] Pooled backward stepwise variable selection was performed on five imputed datasets using variables deemed potentially useful in a clinical predictive tool (R package psfmi, v1.4.0). Variables associated with the outcome were selected across five imputed datasets using Rubin's Rules for variable selection. Continuous variables were modelled using restricted cubic splines. The continuous variables contributing to model performance were included in predictive models as piecewise linear splines for improved interpretation and clinical utility (R package: rms, v6.7.1). Variable selection was optimised for settings with and without laboratory capacity, to support implementation across settings with limited access to diagnostics. Examination variables that identified similar features as laboratory measurements (ie, pallor and haemoglobin) were not included among variables for the laboratory model. A model was also developed using the same features as the WHO advanced disease criteria but as continuous measures. Models were transformed for prediction generation and receiver

operator characteristic (ROC) curves were generated (R package pROC, v1.18.4) for each model and compared with the existing WHO criteria for HIV advanced disease for the total area under the curve (AUC). AUCs of the developed models were compared using DeLong's test and adjusted for multiple comparisons using the Holm method. Model calibration was assessed by comparing the intercept and slope of the logistic calibration and assessing the Brier score for each model (R package CalibrationCurves, v2.0.0). Sensitivity, specificity, and positive and negative predictive values were calculated for a range of probabilities of 1-year mortality. Sensitivity analyses were performed to assess the performance of the model by age group, mortality at 3 and 6 months from ART initiation, and with inclusion of children and adolescents living with HIV who were LTFU within 1 year of ART initiation.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The cohort of children and adolescents living with HIV aged 0–19 years enrolled in the COEs included 19 995 individuals. 2253 were removed when ART initiation occurred before enrolment into the clinic and 784 records were removed in children and adolescents living with HIV with an active chart status but without 365 days of follow-up (figure 1). The same approach was taken for 3-month and 6-month outcome evaluations. The analytic cohort included 16 958 records from patients initiated on ART between 2005 and 2020 from COEs in Eswatini, Lesotho, Malawi, Tanzania (Mbeya and Mwanza), and Uganda (appendix p 5). Overall, 13 931 (82·2%) of 16 958 patients were retained in care at 1 year following ART initiation; of those who were not active in care at 1 year, there were 1189 (7·0%) deaths, 493 (2·9%) lost to follow-up, and 1345 (7·9%) transferred out.

The complete, training, and test cohorts are described in table 1. The population was well distributed across clinical sites, the cohort was equally divided between male and female individuals, and there was equal distribution of WHO clinical stages. General examination findings showed a high proportion of malnutrition and anthropometric measurements confirmed frequent malnutrition. Pallor on exam was documented in 435 (2·6%) individuals and oral thrush in 876 (5·2%) individuals. Median values for complete blood count parameters reflected ranges of normal. CD4 cell counts were evaluated as percentages to account for age-related differences in the absolute number. The training set and test set aligned with the complete cohort across all metrics. Imputed datasets showed similar proportions of categorical predictors and medians for continuous predictors (appendix p 6). Outcomes, examination findings, and laboratory values were also similar across sites (appendix p 7).

Variables considered for inclusion in the models are listed in the appendix (p 8). All variables were associated with death by pooled bivariate logistic regression except for sex and the presence of a WHO stage 2 condition. Variable selection was optimised for clinical settings with and without laboratory access (table 2). A model mirroring the variables considered in the WHO advanced HIV criteria was developed using continuous measures

for age and CD4 percentage (table 2). All included continuous variables had non-linear relationships with the outcome of interest; the relationship was modelled using restricted cubic splines to guide knot placement for linear splines that were included in the predictive models (figure 2).

Pooled multivariable logistic regression for the laboratory model training set (table 2) showed a reduction in the odds of death within 1 year of ART initiation that was associated with increasing age up to the age of 3 years and an increase in the odds of death with increasing age for those aged 4 years and older. WHO stage 3 and WHO stage 4 conditions were strongly associated with death when compared with the reference group (WHO stage 1). Each unit increase in CD4 percentage was associated with a reduction in the odds of death from 0% to 30%; there was no association with increasing CD4 percentage above 30%. Increases in BMI age-adjusted Z score were associated with a decreasing odds of death up to a Z score of 0; increases in BMI above a Z score of 0 were not associated with death. Exam features that were retained in the model included the presence of oedema, respiratory distress, and abnormal muscle tone. Abnormal laboratory measurements from a complete blood count were associated with death. Every unit increase in haemoglobin from 0–12 g/dL was associated in a reduction in the odds of death, and with an increase above 12 g/dL. A similar pattern was observed for platelets below and above 350×10^9/L.

In the exam-based model (table 2), the effect of age; WHO stage; and the examination features of oedema, abnormal muscle tone, and respiratory distress were similar to the laboratory model. The presence of wasting on examination was associated with an increased odds of death. Pallor on examination was associated with an increased odds of death, as was the presence of oral thrush. The advanced HIV continuous model (table 2), retained all variables and showed similar associations for the included variables.

The predictive accuracy of the laboratory, exam, and advanced HIV continuous models generated from the test set were reduced slightly from the training set (appendix p 8) and are summarised by ROC curves in figure 3. The AUC in the test set was 0·822 (95% CI 0·800–0·845) for the laboratory model, 0·801 (0·779–0·824) for the exam model, 0·785 (0·762–0·808) for the advanced HIV continuous variable model, and 0·606 (0·595–0·617) for the WHO advanced HIV criteria. The laboratory model was superior to the exam model (p=0·002), advanced HIV continuous model (p<0·0001), and WHO advanced HIV model (p<0·0001). When the cohort was restricted by age, the AUC for each model was comparable in children aged 0–11 years and in children aged 0–4 years (figure 3). Imputation using median laboratory values did not alter the AUC for the laboratory model (0·82 [0·80–0·84]).

The AUCs of all models were similar in the test set when excluding one site, when predicting death within 3 or 6 months of ART initiation, and when including children and adolescents who were LTFU in the model (appendix pp 9–10). The models also performed similarly when stratified by children and adolescents initiating ART between 2005 and 2011 versus 2012 and 2020 (appendix p 11). When evaluated with a time-dependent cox proportional hazards model, the c-statistic was also similar (appendix p 11).

Model calibration is equally important to discrimination, and each model was well calibrated when evaluated in the test set against the empirical probability of death with slopes ranging from 0·94 to 0·97 (appendix p 12). The models remained well calibrated when the data was restricted by site and to children aged 0–4 and 0–11 years (appendix pp 13–16).

Diagnostic accuracy measurements of each model are displayed in table 3, with the predicted probability of death ranging between 2% and 6%. A threshold of between 3% and 4% aligns with a sensitivity of approximately 90% for all models. The accuracy of the laboratory, exam, and advanced HIV continuous models was substantially higher than the WHO advanced HIV criteria, reflecting the increased specificity of the models. The negative predictive value of each model remained above 97%.

Discussion

In this multinational cohort of 16 958 children and adolescents living with HIV initiating ART in five sub-Saharan African countries, we have developed and internally validated three mortality prediction scores. The predictive accuracy of these models for death within the first year following ART initiation is substantially higher than the current WHO advanced HIV criteria.

This large generalisable dataset confirmed risk factors that have been previously identified as being associated with mortality in smaller studies. These risk factors include young age,[23] malnutrition,[8] immunosuppression, and the presence or history of a WHO clinical stage 3 or 4 condition.[8,9,23] We were also able to identify several physical exam features that were associated with death within 1 year of ART, including respiratory distress, pallor, wasting, abnormal muscle tone, jaundice, developmental delay, stunting, and oral thrush. Aiming to develop a mortality risk score that can be implemented in low-resource settings, we limited these physical exam features to those that can be easily identified through a rapid visual examination. An abnormal complete blood count was associated with mortality, with a low haemoglobin being strongly associated with mortality, as has previously been reported in children[24] and adults.[16]

Mortality prediction tools in adults living with HIV have included age, CD4 cell count, haemoglobin concentration, aspartate and alanine transaminase concentration, platelet count, creatinine concentration, and hepatitis C status as clinical predictors.[16] Another collaborative cohort of adults initiating ART, predicting outcomes up to 5 years from ART initiation, included 19 cohorts from across Europe and North America, but none from sub-Saharan Africa.[25] These existing scores are more reliant on laboratory assessments than is practical in resource-limited settings where laboratory assessments beyond a complete blood count and CD4 count are rarely available. The complete blood count was only available in 70% of our cohort, indicating the need for complementary non-laboratory dependent mortality-risk scores. As such, we also assessed a model focused on easily defined visual examination findings, excluding CD4 counts, other laboratory assessments, and BMI-for-age Z score. Without these features, the model had an inferior AUC compared with the laboratory model; nevertheless, the AUC was comparable to the advanced HIV continuous model. This finding suggests that even in the absence of CD4 counts and other laboratory measures, mortality

prediction in children and adolescents living with HIV is still possible. Clinical providers in remote settings could apply the exam model to new clients, even before obtaining laboratory results.

Four previous studies have derived mortality prediction scores in children living with HIV. The Full PASS and Simple PASS scores were derived from a study population based in the USA, included children pre-ART, and are probably less applicable to high-burden settings.[11,12] Another study derived a model with an AUC of 0·79 using HIV-related symptoms or conditions, CD4 count, weight-for-age Z score, and total lymphocyte counts as categorical predictors, but was from a single centre in sub-Saharan Africa.[13] The most generalisable study evaluated children initiating ART predominantly in South Africa, but also included children initiating ART in Malawi, Zimbabwe, and Zambia.[14] This model had an AUC of 0·753 and included age, CD4 percentage, WHO stage, anaemia, and weight-for-age Z score. The increased discriminatory capacity of our model is probably attributable to the use of additional laboratory measures and BMI. Overall, these previous models derived similar predictors to our models, and given the consistency across multiple settings and the high-discriminatory capacity of the models, additional consideration should be given to an impact assessment of a mortality prediction tool on clinical decision making and outcomes in children and adolescents living with HIV.

The increased discriminatory power of our models was also attributable to the retention of continuous variables, all of which had non-linear relationships with the outcome of interest. Even the advanced HIV continuous model, which contained the same variables as the advanced HIV criteria but with CD4 percentage and age modelled using linear splines, had a substantially higher AUC than the categorical model based on WHO advanced HIV criteria. In the past, integration of continuous variables required dependency on paper nomograms resulting in substantial feasibility concerns; however, with internet and smartphone access for health-care providers, even in remote settings, this is no longer a substantial detriment if the contributions of continuous variables are calculated automatically. A model that is generalisable across multiple country contexts might also reduce the cost of design, development, and implementation when compared to developing context-specific models.

Our data indicate that young age is a major risk factor for mortality in children and adolescents living with HIV; however, identifying all children younger than 5 years presenting for ART initiation as having an equally high risk for mortality, as is currently the case based on WHO advanced HIV guidance, does not support clinicians to make effective decisions about which children could benefit from more frequent follow-ups or referral to higher levels of care. These interventions often require increased support through transport funding or home visits,[26] the availability of which is constrained in many settings throughout sub-Saharan Africa. With sensitivity set at a minimum of 90%, the models were more specific than advanced HIV criteria, correctly specifying approximately 1000 more children than the advanced HIV criteria would have identified who survived and were retained in care. This differentiation could allow for more resources to be directed towards higher risk children; further, the mortality risk threshold could be adjusted to focus on the highest risk children depending on resources available for service interventions.

High-quality services for children living with HIV include outreach services,[27,28] peer support,[29,30] financial enablers to defray transport costs when needed,[31] nutritional support,[32] and psychosocial counselling.[33] These additional services can reduce morbidity and mortality in children and adolescents with HIV, but they are also costly, remain absent in many care settings, and are typically provided by clinical centres with resources that fall outside of those provided routinely by Ministries of Health.[34] Clinical prediction tools could help direct these services to the clients who need them most. The models described perform equally well or better in predicting mortality within 3 and 6 months to 1 year, and could be used to provide additional targeted services within those timeframes.

This study is subject to limitations, one of which was internal validation. This limitation was potentially mitigated by the size and generalisability of the dataset. Although the COE in this study might provide a best-case scenario with respect to client outcomes, all sites function within the Ministry of Health system adhere to national guidelines for laboratory testing, and are subject to the limitations common to other facilities in the region, such as medication stock ruptures, staff shortages, and limited resources for supportive services. Further, as with all retrospective electronic medical record data, some variables in our dataset had a substantial proportion of missing values, and we cannot exclude an element of misattributed data entry. The model predictions were robust across different age strata, but the models are most applicable for children and adolescents with presumptively vertical acquisition of HIV, as compared with older sexually active adolescents. Finally, sparse data limited calibration at a predicted probability of mortality of over 40%; however, this has little effect on the use of the models since mortality risk is rarely greater than 40% in most clinical settings.

In conclusion, mortality risk prediction using the laboratory, exam, and advanced HIV continuous models could guide informed clinical decision making on patient-centred care (DSD models) to reduce mortality among children and adolescents living with HIV initiating ART, particularly in remote health-care settings. Although the risk of mortality is high in all children and adolescents living with HIV initiating ART, we have shown that commonly available clinical and laboratory features can provide valuable information to guide clinicians on which children are at the highest risk for death. Future steps include external validation of the mortality risk prediction scores and an impact assessment—with a mobile application—on the clinical outcomes of children and adolescents living with HIV and initiating ART.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data sharing

Individual participant data that underlie the results in the text, tables, and figures will be available after de-identification, as will the data analysis plan. The data will be available beginning 6 months and ending 3 years after publication. Data will be shared with investigators providing a methodologically sound protocol for individual patient meta-analysis that will be reviewed by relevant ethics boards in each country. Requests can be submitted to the corresponding author, which will be followed by review at each clinical site and requestors will need to sign country-specific data access agreements.

References

1. Bekker LG, Siberry GK, Hirnschall G. Ensuring children and adolescents are not left behind. J Acquir Immune Defic Syndr 2018; 78 (suppl 1): S1–2. [PubMed: 29994912]
2. Kim MH, Wanless RS, Caviness AC, et al. Multimonth prescription of antiretroviral therapy among children and adolescents: experiences from the Baylor International Pediatric AIDS Initiative in 6 African countries. J Acquir Immune Defic Syndr 2018; 78 (suppl 2): S71–80. [PubMed: 29994828]
3. Bacha JM, Aririguzo LC, Mng'ong'o V, et al. The Standardized Pediatric Expedited Encounters for ART Drugs Initiative (SPEEDI): description and evaluation of an innovative pediatric, adolescent, and young adult antiretroviral service delivery model in Tanzania. BMC Infect Dis 2018; 18: 1–9. [PubMed: 29291713]
4. UNAIDS. UNAIDS Global HIV & AIDS Statistics. https://www.unaids.org/en/resources/fact-sheet#:~:text=38·0%20million%20%5B31·6%20million%E2%80%9344·5,AIDS%2Drelated%20illnesses%20in%202019 (accessed July 29, 2020).
5. McNairy ML, Abrams EJ, Rabkin M, El-Sadr WM. Clinical decision tools are needed to identify HIV-positive patients at high risk for poor outcomes after initiation of antiretroviral therapy. PLoS Med 2017; 14: e1002278–6. [PubMed: 28419097]
6. Siika A, McCabe L, Bwakura-Dangarembizi M, et al. Late presentation with HIV in Africa: phenotypes, risk, and risk stratification in the REALITY trial. Clin Infect Dis 2018; 66 (suppl 2): S140–46. [PubMed: 29514235]
7. Kabue MM, Buck WC, Wanless SR, et al. Mortality and clinical outcomes in HIV-infected children on antiretroviral therapy in Malawi, Lesotho, and Swaziland. Pediatrics 2012; 130: e591–99. [PubMed: 22891234]
8. Judd A, Chappell E, Turkova A, et al. Long-term trends in mortality and AIDS-defining events after combination ART initiation among children and adolescents with perinatal HIV infection in 17 middle and high-income countries in Europe and Thailand: a cohort study. PLoS Med 2018; 15: e1002491–19. [PubMed: 29381702]
9. Fenner L, Brinkhof MWG, Keiser O, et al. Early mortality and loss to follow-up in HIV-infected children starting antiretroviral therapy in Southern Africa. J Acquir Immune Defic Syndr 2010; 54: 524–32. [PubMed: 20588185]
10. Buck WC, Olson D, Kabue MM, et al. Risk factors for mortality in Malawian children with human immunodeficiency virus and tuberculosis co-infection. Int J Tuberc Lung Dis 2013; 17: 1389–95. [PubMed: 24125439]
11. Seage GR, Buchacz K, Weinberg GA, Patel K, McIntosh K, Dankner WM. The Pediatric AIDS Severity Score (PASS): a multidimensional AIDS-severity adjustment for pediatric HIV infection. J Acquir Immune Defic Syndr 2006; 43: 603–10. [PubMed: 17003692]
12. Patel K, Weinberg GA, Buchacz K, McIntosh K, Dankner WM, Seage GR. Simple Pediatric AIDS Severity Score (PASS): a pediatric severity score for resource-limited settings. J Acquir Immune Defic Syndr 2006; 43: 611–17. [PubMed: 17003691]
13. Nugent J, Edmonds A, Lusiama J, Thompson D, Behets F. Predicting mortality in HIV-infected children initiating highly active antiretroviral therapy in a resource-deprived setting. Pediatr Infect Dis J 2014; 33: 1148–55. [PubMed: 24945879]

14. Davies MA, May M, Bolton-Moore C, et al. Prognosis of children with HIV-1 infection starting antiretroviral therapy in Southern Africa: a collaborative analysis of treatment programs. Pediatr Infect Dis J 2014; 33: 608–16. [PubMed: 24378936]
15. Mocroft A, Ledergerber B, Zilmer K, et al. Short-term clinical disease progression in HIV-1-positive patients taking combination antiretroviral therapy: the EuroSIDA risk-score. AIDS 2007; 21: 1867–75. [PubMed: 17721094]
16. Tate JP, Justice AC, Hughes MD, et al. An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS 2013; 27: 563–72. [PubMed: 23095314]
17. WHO. Package of care for children and adolescents with advanced HIV disease: stop AIDS. Technical Brief 2020. https://www.who.int/publications/i/item/9789240008045 (accessed June 1, 2023).
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370: 1453–57. [PubMed: 18064739]
19. Kay A, Reyes JM, Devezin T, et al. Optimal timing of antiretroviral therapy initiation in children and adolescents with HIV-associated pulmonary tuberculosis. Clin Infect Dis 2022; 76: 10–17.
20. Mandalakas AM, Kay AW, Bacha JM, et al. Tuberculosis among children and adolescents at HIV treatment centers in sub-Saharan Africa. Emerg Infect Dis 2020; 26: 2933–43. [PubMed: 33219815]
21. Ardura-Garcia C, Feldacker C, Tweya H, et al. Implementation and operational research: early tracing of children lost to follow-up from antiretroviral treatment: true outcomes and future risks. J Acquir Immune Defic Syndr 2015; 70: e160–67. [PubMed: 26218409]
22. Tang F, Ishwaran H. Random forest missing data algorithms. Stat Anal Data Min 2017; 10: 363–77. [PubMed: 29403567]
23. Mutanga JN, Mutembo S, Ezeamama AE, et al. Long-term survival outcomes of HIV infected children receiving antiretroviral therapy: an observational study from Zambia (2003–2015). BMC Public Health 2019; 19: 115. [PubMed: 30691416]
24. Aguilar G, Miranda AE, Rutherford GW, et al. Mortality rate and predictors in children under 15 years old who acquired HIV from mother to child transmission in Paraguay. AIDS Behav 2018; 22 (suppl 1): 99–104. [PubMed: 29455264]
25. May MT, Ingle SM, Costagliola D, et al. Cohort profile: Antiretroviral Therapy Cohort Collaboration (ART-CC). Int J Epidemiol 2014; 43: 691–702. [PubMed: 23599235]
26. Busza J, Dauya E, Bandason T, Mujuru H, Ferrand RA. “I don’t want financial support but verbal support.” How do caregivers manage children’s access to and retention in HIV care in urban Zimbabwe? J Int AIDS Soc 2014; 17: 18839. [PubMed: 24815595]
27. Braitstein P, Songok J, Vreeman R, et al. ‘Wamepotea’ (they have become lost): outcomes of HIV-positive and HIV-exposed children lost to follow-up from a large HIV treatment program in western Kenya. J Acquir Immune Defic Syndr 2011; 57: e40–46. [PubMed: 21407085]
28. Herce ME, Chagomerana MB, Zalla LC, et al. Community-facility linkage models and maternal and infant health outcomes in Malawi’s PMTCT/ART program: a cohort study. PLoS Med 2021; 18: e1003780. [PubMed: 34534213]
29. Igumbor JO, Ouma J, Otwombe K, et al. Effect of a mentor mother programme on retention of mother-baby pairs in HIV care: a secondary analysis of programme data in Uganda. PLoS One 2019; 14: e0223332. [PubMed: 31609974]
30. Willis N, Napei T, Armstrong A, et al. Zvandiri-bringing a differentiated service delivery program to scale for children, adolescents, and young people in Zimbabwe. J Acquir Immune Defic Syndr 2018; 78 (suppl 2): S115–23. [PubMed: 29994833]
31. Bosma CB, Toromo JJ, Ayers MJ, Foster ED, McHenry MS, Enane LA. Effects of economic interventions on pediatric and adolescent HIV care outcomes: a systematic review. AIDS Care 2024; 36: 1–16. [PubMed: 37607246]
32. Sunguya BF, Poudel KC, Mlunde LB, et al. Ready to Use Therapeutic Foods (RUTF) improves undernutrition among ART-treated, HIV-positive children in Dar es Salaam, Tanzania. Nutr J 2012; 11: 60. [PubMed: 22931107]

33. Brouwer CNM, Lok CL, Wolffers I, Sebagalls S. Psychosocial and economic aspects of HIV/AIDS and counselling of caretakers of HIV-infected children in Uganda. AIDS Care 2000; 12: 535–40. [PubMed: 11218540]

34. Vreeman RC, Yiannoutsos CT, Yusoff NKN, et al. Global HIV prevention, care and treatment services for children: a cross-sectional survey from the International Epidemiology Databases to Evaluate AIDS (IeDEA) consortium. BMJ Open 2023; 13: e069399.

Research in context

Evidence before this study

The risk of mortality in children and adolescents living with HIV has been linked to a host of clinical and laboratory markers, such as CD4 cell count, age, nutritional status, and blood cell counts. Currently, however, there are no prediction tools available that clinicians can use to individualise care and treatment based on the risk of death in children initiating antiretroviral therapy. HIV care in high-burden settings is becoming more decentralised; an evidence-based mortality prediction tool could be used by health workers to guide referrals, follow-up, and distribution of resources. We searched PubMed on Jan 9, 2024 for articles published from database inception to Dec 13, 2023 containing the terms “mortality prediction score” and “HIV” in any language. We restricted the search to children and adolescents aged 0–18 years. The search generated 88 results, including four studies predicting mortality in children living with HIV. Two studies were from a high-resource environment and included participants before ART initiation, and another study was from a single centre, suggesting limited applicability and generalisability. The area under the curve of the models ranged from 0·753 to 0·841. The categorical predictors for the most generalisable model derived from children in southern Africa included CD4 percentage, WHO stage, weight-for-age Z score, and anaemia.

Added value of this study

This study describes the derivation of a mortality prediction tool from a clinical population evenly distributed between five high HIV burden, low-resource clinical settings. Previous predictive scores have been derived primarily from higher resourced environments (USA or South Africa) or single centres. The predictive models derived in this study have higher areas under the curve than those previously developed, can be implemented with and without laboratory data, and can be used to support differentiated service delivery.

Implications of all the available evidence

An impact assessment of a mortality prediction tool in children living with HIV should be considered to support differentiated service delivery in an era of increasingly decentralised HIV care in high-burden settings.

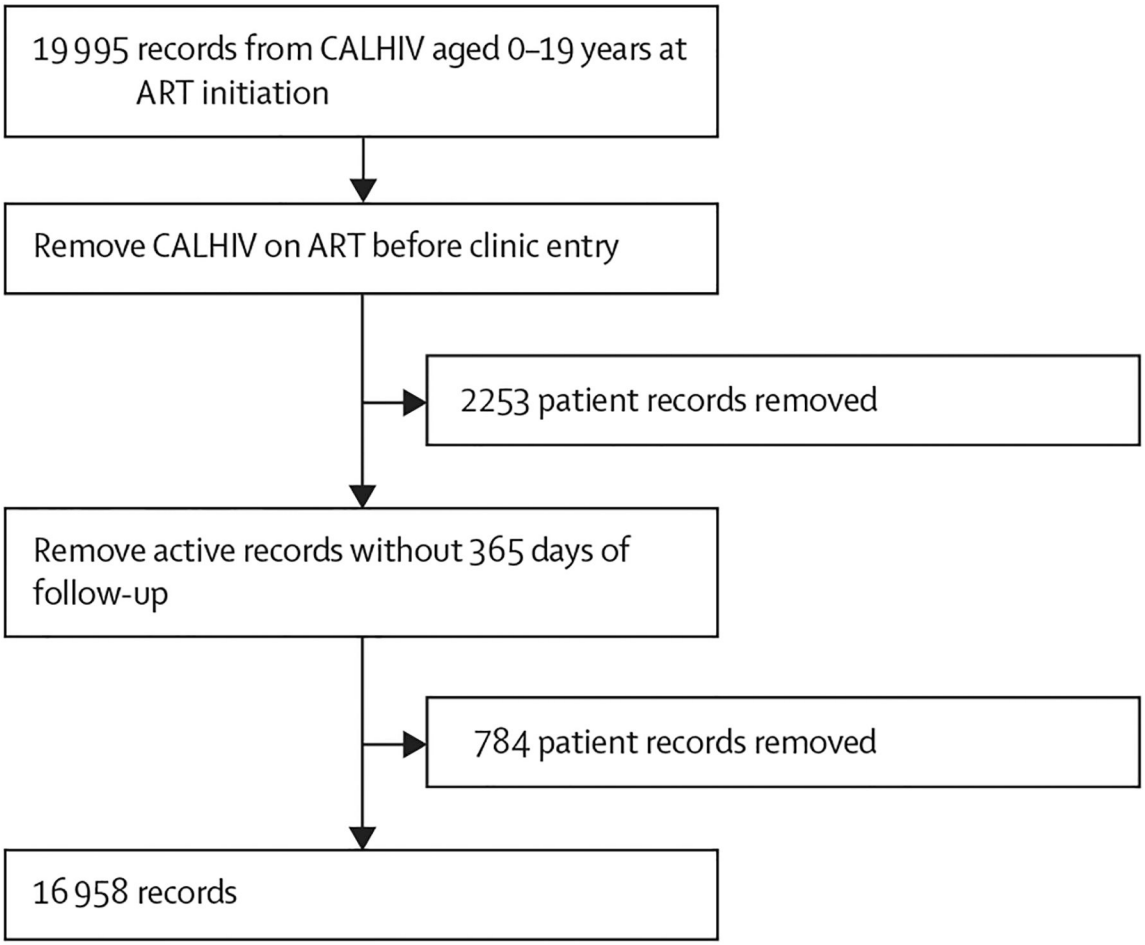


Figure 1: STROBE diagram of record identification and exclusions from the primary analysis
ART=antiretroviral therapy. CALHIV=children and adolescents living with HIV.

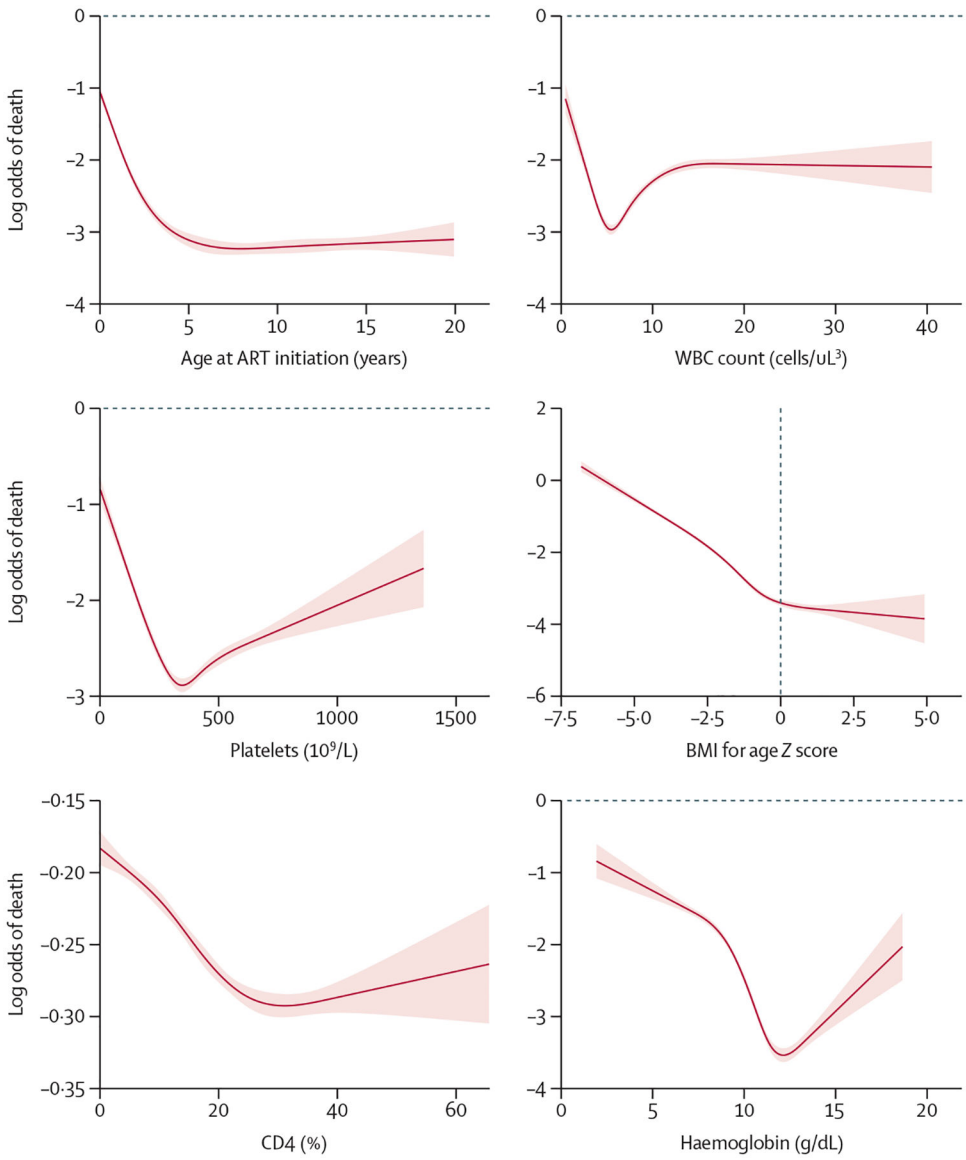
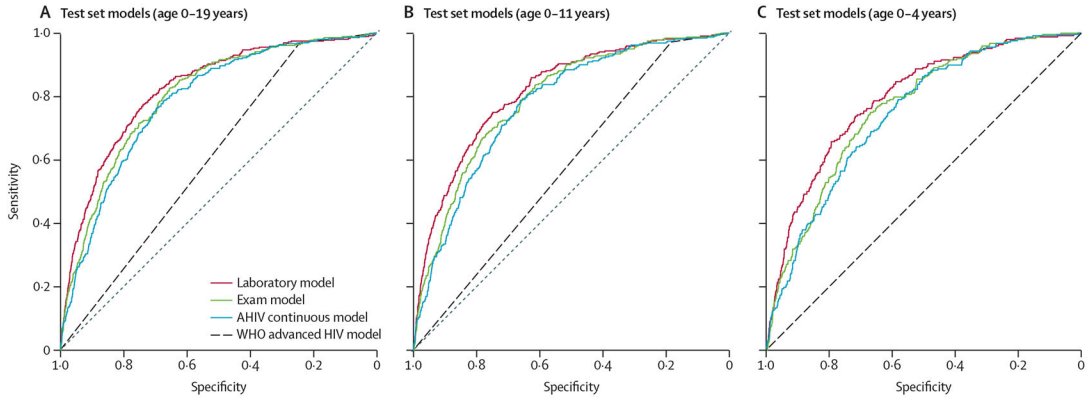


Figure 2: Relationship between continuous variables included in the models and the log odds of the outcome of interest (death within one year of ART initiation)

ART=antiretroviral therapy. WBC=white blood cells.



Model	Age 0–19 years AUC	95% CI	DeLong test	Age 0–11 years AUC	95% CI	DeLong test	Age 0–4 years AUC	95% CI	DeLong test
Laboratory	0·822	0·800–0·845	Ref	0·813	0·789–0·837	Ref	0·793	0·764–0·821	Ref
Exam	0·801	0·779–0·824	0·002	0·793	0·768–0·817	0·006	0·761	0·732–0·795	0·001
AHIV continuous	0·785	0·762–0·808	<0·0001	0·775	0·750–0·800	<0·0001	0·744	0·715–0·774	<0·0001
WHO advanced HIV	0·606	0·595–0·617	<0·0001	0·577	0·567–0·589	<0·0001	..	..	..

Figure 3: Test set receiver operating characteristic curves displaying the AUC for the laboratory-based, exam-based, and advanced HIV continuous models compared with the WHO advanced HIV criteria for the complete cohort (A), children aged 0–11 years (B), and children aged 0–4 years (C)

The receiver operating characteristic curves are supported by the table showing the numerical AUC, 95% CI, and a comparison using the DeLong test of the various models with adjustment for multiple comparisons using the Holm method. AUC=area under the curve.

Table 1:

Clinical characteristics of the complete dataset, training, and test datasets

	Complete (N=16 958)	Training (N=11 871)	Test (N=5087)
Sex			
Male	8253 (48·7%)	5833 (49·1%)	2420 (47·6%)
Female	8705 (51·3%)	6038 (50·9%)	2667 (52·4%)
Site			
Eswatini	2428 (14·3%)	1684 (14·2%)	744 (14·6%)
Lesotho	3045 (18·0%)	2099 (17·7%)	946 (18·6%)
Malawi	3599 (21·2%)	2536 (21·4%)	1063 (20·9%)
Tanzania (Mbeya)	2008 (11·8%)	1429 (12·0%)	579 (11·4%)
Tanzania (Mwanza)	1046 (6·2%)	735 (6·2%)	311 (6·1%)
Uganda	4832 (28·5%)	3388 (28·5%)	1444 (28·4%)
WHO stage			
1	3986 (23·5%)	2746 (23·1%)	1240 (24·4%)
2	2153 (12·7%)	1546 (13·0%)	607 (11·9%)
3	3667 (21·6%)	2561 (21·6%)	1106 (21·7%)
4	3308 (19·5%)	2328 (19·6%)	980 (19·3%)
Missing	3844 (22·7%)	2690 (22·7%)	1154 (22·7%)
Outcome			
Retained in care	13 931 (82·2%)	9752 (82·1%)	4179 (82·2%)
Transferred	1345 (7·9%)	941 (7·9%)	404 (7·9%)
Lost to follow-up	493 (2·9%)	348 (2·9%)	145 (2·9%)
Died	1189 (7·0%)	830 (7·0%)	359 (7·1%)
Wasting	3042 (17·9%)	2138 (18·0%)	904 (17·8%)
Missing	1482 (8·7%)	1053 (8·9%)	429 (8·4%)
General oedema	160 (0·9%)	111 (0·9%)	49 (1·0%)
Missing	1482 (8·7%)	1053 (8·9%)	429 (8·4%)
Pallor	435 (2·6%)	302 (2·5%)	133 (2·6%)
Missing	1482 (8·7%)	1053 (8·9%)	429 (8·4%)
Oral thrush	876 (5·2%)	617 (5·2%)	259 (5·1%)
Missing	2242 (13·2%)	1568 (13·2%)	674 (13·2%)
Abnormal muscle tone	144 (0·8%)	103 (0·9%)	41 (0·8%)
Missing	3230 (19·0%)	2278 (19·2%)	952 (18·7%)
Jaundice	14 (0·1%)	10 (0·1%)	4 (0·1%)
Missing	1482 (8·7%)	1053 (8·9%)	429 (8·4%)
Age at ART initiation, years	5·1 (1·6 to 10·3)	5·00 (1·5 to 10·3)	5·2 (1·6 to 10·4)
BMI Z score	−0·7 (−1·8 to 0·2)	−0·7 (−1·8 to 0·2)	−0·7 (−1·8 to 0·2)
Missing	1231 (7%)	858 (7·2%)	373 (7·3%)
CD4 percentage	17·0 (11·0 to 25·0)	17·0 (11·0 to 25·0)	18·9 (11·0 to 25·0)
Missing	4104 (24·2%)	2866 (24·1%)	1238 (24·3%)
Haemoglobin (g/dL)	10·4 (9·0 to 11·6)	10·3 (9·0 to 11·6)	10·2 (9·1 to 11·5)

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	Complete (N=16 958)	Training (N=11 871)	Test (N=5087)
Missing	4580 (27%)	4580 (27%)	1374 (27·5%)
WBC count (cells/uL^3)	7·1 (5·0 to 10·3)	7·2 (5·0 to 10·4)	7·0 (5·0 to 10·2)
Missing	4824 (28·4%)	3384 (28·5%)	1440 (28·3%)
Platelet count (10^9/L)	336 (244 to 441)	333 (241 to 440)	342 (250 to 443)
Missing	5436 (32%)	3817 (32·1%)	1619 (31·8%)

Data shown are n (%) or median (IQR). ART=antiretroviral therapy. WBC=white blood cells.

Table 2:

Pooled multivariable odds ratios of variables selected for the laboratory-based model, the exam-based model, and the advanced HIV continuous model computed across five imputed datasets

	Odds ratio	95% CI
Laboratory-based model		
Age 0–3 years *	0·72	0·66 to 0·79
Age 4 years and older *	1·39	1·24 to 1·55
WHO stage 2	0·98	0·66 to 1·47
WHO stage 3	1·56	1·12 to 2·17
WHO stage 4	2·94	2·18 to 3·95
CD4% (0–30%) *	0·96	0·95 to 0·97
CD4% (>30%) *	1·04	1·00 to 1·09
BMI Z score for age (≤0) *	0·74	0·69 to 0·78
BMI Z score for age (>0) *	1·26	0·96 to 1·64
Exam features		
Generalised oedema	5·10	3·11 to 8·36
Respiratory distress	2·32	1·33 to 4·05
Abnormal muscle tone	1·95	1·17 to 3·26
Full blood count results		
Haemoglobin (0–12 g/dL) *	0·86	0·81 to 0·92
Haemoglobin (≥13 g/dL) *	1·39	1·10 to 1·75
Platelet count (0–350 × 10^9/L) *	1·00	1·00 to 1·00
Platelet count (≥351 × 10^9/L) *	1·00	1·00 to 1·01
WBC count (0–4 cells/uL^3) *	0·76	0·63 to 0·93
WBC count (5–12 cells/uL^3) *	1·31	1·06 to 1·62
WBC count (≥13 cells/uL^3) *	0·99	0·93 to 1·05
Exam-based model		
Age 0–3 years *	0·66	0·61 to 0·71
Age 4 years and older *	1·57	1·42 to 1·74
WHO stage 2	1·04	0·71 to 1·52
WHO stage 3	1·92	1·40 to 2·63
WHO stage 4	4·13	3·11 to 5·50
Exam features		
Wasting	1·94	1·63 to 2·32
Generalised oedema	4·04	2·56 to 6·38
Pallor	1·68	1·22 to 2·31
Respiratory distress	2·10	1·22 to 3·63
Abnormal muscle tone	2·01	1·22 to 3·31
Oral thrush	1·42	1·10 to 1·83
Advanced HIV continuous model		

	Odds ratio	95% CI
Age 0–3 years *	0·60	0·55 to 0·64
Age 4 years and older *	1·72	1·56 to 1·90
WHO stage 2	0·98	0·67 to 1·43
WHO stage 3	2·07	1·52 to 2·80
WHO stage 4	5·98	4·62 to 7·73
CD4% (0–30%) *	0·95	0·94 to 0·96
CD4% (>30%) *	1·07	1·02 to 1·11

Sex, stunting, oral thrush, jaundice, and developmental delay did not improve the model by backward stepwise regression and were removed from the model. WBC=white blood cells.

* Continuous variables are represented as the change in the odds of death per unit increase in the variable and are modelled as linear splines based on the log odds association with the outcome of interest.

Table 3:

Accuracy of all models for mortality prediction in the test set with a mortality risk threshold ranging from 2 to 6%

	True positive	False negative	False positive	True negative	Accuracy	Sensitivity	Specificity	PPV	NPV
Laboratory model									
2·0%	344	15	2763	1416	0·39	0·96	0·34	0·11	0·99
3·0%	328	31	2106	2073	0·53	0·91	0·50	0·13	0·99
4·0%	312	47	1696	2483	0·62	0·87	0·59	0·16	0·98
5·0%	301	58	1404	2775	0·68	0·84	0·66	0·18	0·98
6·0%	284	75	1181	2998	0·72	0·79	0·72	0·19	0·98
Exam model									
2·0%	347	12	3181	998	0·30	0·97	0·24	0·10	0·99
3·0%	333	26	2434	1745	0·46	0·93	0·42	0·12	0·99
4·0%	319	40	1888	2291	0·58	0·89	0·55	0·14	0·98
5·0%	308	51	1654	2525	0·62	0·86	0·60	0·16	0·98
6·0%	286	73	1359	2820	0·68	0·80	0·67	0·17	0·97
Advanced HIV continuous model									
2·0%	347	12	3073	1106	0·32	0·97	0·26	0·10	0·99
3·0%	332	27	2464	1715	0·45	0·92	0·41	0·12	0·98
4·0%	319	40	2047	2132	0·54	0·89	0·51	0·13	0·98
5·0%	302	57	1728	2451	0·61	0·84	0·59	0·15	0·98
6·0%	288	71	1453	2726	0·66	0·80	0·65	0·17	0·97
Advanced HIV binary model									
2·0–6·0%	348	11	3162	1017	0·30	0·97	0·24	0·10	0·99

Data shown are calculated diagnostic accuracy estimates for each model across a range of mortality risk thresholds. NPV=negative predictive value. PPV=positive predictive value.