A New Health Care Index independently predicts 12-month mortality among HIV positive individuals diagnosed with tuberculosis

Ashley Roen, MA. UCL Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, University College London, London, United Kingdom.

Daria Podlekareva, MD. Copenhagen HIV Programme, University of Copenhagen, Denmark.

Robert F Miller, MBBS, Professor. UCL Centre for Clinical Research in Infection and Sexual Health, Institute for Global Health, University College London, London, United Kingdom.

University College London, London, UK

Frank A Post, PhD, Professor. Kings College Hospital NHS Foundation Trust, London, United Kingdom.

Amanda Mocroft, MSc, Professor. UCL Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, University College London, London, United Kingdom.

Ole Kirk, MD. Copenhagen HIV Programme, University of Copenhagen, Denmark. Rigshospitalet, Copenhagen, Denmark.

Introduction

Local levels of health care provision and resource availability have been strongly linked with survival rates of HIV-positive individuals with tuberculosis (TB)[1-3]. These factors include prompt diagnosis of TB coupled with drug susceptibility testing (DST), timely initiation of TB treatment, and adequate HIV management and care, including immune health monitoring and timely initiation of combination antiretroviral therapy (cART). Our previous report used retrospective data from a cohort of HIV-positive individuals with TB diagnosed between 2004 and 2006 and found that DST, a TB treatment regimen containing at least rifampicin, isoniazid and pyrazinamide, and use of cART were all significantly associated with a reduction in 12-month mortality. We combined these factors into a Health Care Index (HCI)[1] designed to be used in planning and evaluation of health care interventions across high- and low-income settings.

Subsequently, there have been several changes in the management and care of patients co-infected with TB and HIV. Rapid molecular diagnostic methods which simultaneously provide results for rifampicin susceptibility, enabling personalized and prompt prescription of anti-tuberculosis medication are increasingly widely available. For this reason, in 2010, the WHO suggested that GeneXpert should be the first test conducted when TB is suspected[4]. As assessment of genotypic resistance in many settings has allowed clinicians to tailor initial therapy, rather than waiting for culture-based drug susceptibility tests, optimal initial treatment may no longer be a RHZ-based regimen, if resistance is rapidly identified. This is likely to be of greater importance in settings with a high prevalence of multi-drug resistant TB (MDR-TB).

Over the last few years there has been better access to several new (bedaquiline, delamanid, linezolid) and older drugs (clofazimine, moxifloxacin) for those with MDR-TB which has broadened initial TB treatment options in Western and Southern Europe, but probably not to the same extent in Eastern Europe, or in South America[5]. Therefore, the number of TB drugs, or the number of "presumed active" drugs prescribed for an individual might be a better prognostic indicator than use of an RHZ-based treatment regimen. The importance of starting cART soon after diagnosis of TB is well established[6,7]. Additionally, initiation of co-trimoxazole prophylaxis may also be a marker of better health care engagement, as co-trimoxazole in combination with cART is recommended for HIV-positive individuals with low CD4 cell counts, or in settings with high burdens of infectious disease, and has been associated with reduced

mortality among TB-HIV co-infected individuals[8-10]. Finally, the frequency of CD4 cell count and HIV-RNA measurements are indicators of effective management of HIV infection as well as underlying clinical resources[11,12].

For these reasons, we aimed to update our previous HCI to coincide with recent changes in diagnostics, drug susceptibility testing, and in clinical monitoring practices. We therefore sought to re-evaluate the previously generated HCI in a prospective cohort of TB-HIV co-infected individuals and additionally, to asses if additional factors that parallel recent changes in TB-HIV health care management provided added value in predicting health care utilization and had impact on mortality.

Methods

Data

The TB:HIV Study is a multicentre prospective cohort study of over 1400 HIV-positive patients co-infected with TB accessing care from 62 clinics in 19 countries spanning Eastern, Western, and Southern Europe as well as Latin America[13]. Adults over 16 years living with HIV and diagnosed with TB between 2011 and 2013 were enrolled. Further details are available at https://www.chip.dk/Studies/TBHIV/About.

Health Care Index

The focus of the index is to evaluate aspects of provided health care to individuals with TB and HIV, rather than disease-specific characteristics. Our previous study investigated five major characteristics of health care provision which were based on BHIVA and NIH guidelines for management of TB-HIV co-infected individuals[2,3]. The characteristics were:

1. World Health Organization (WHO) defined definite diagnosis of TB: culture-confirmed disease due to *Mycobacterium tuberculosis* and/or at least one sputum smear examination positive for acid-fast bacilli (AFB)
2. Performance of DST for *M. tuberculosis* within one month of TB diagnosis
3. Inclusion of a rifamycin (R), isoniazid (H, INH) and pyrazinamide (Z, PZA) in the initial TB treatment regimen
4. At least one CD4 cell count measurement obtained between six months before and one month after TB diagnosis

5. Initiation of cART (a combination of at least three antiretroviral drugs from any class) either before, or up to one month after TB diagnosis.

In this study, we investigated four additional measures of health care engagement.

6. Use of co-trimoxazole prophylaxis (either before, or up to one month after TB diagnosis)
7. A plasma HIV-RNA measurement obtained between six months before and one month after TB diagnosis
8. Total number of drugs (irrespective of DST results) prescribed within the initial TB treatment regimen (within one month before or one month after TB diagnosis)
9. Total number of known active TB drugs in the TB treatment regimen (within one month before or one month after TB diagnosis)

Initial TB treatment regimens were considered 'known active' if the *M. tuberculosis* isolate was found to be susceptible by DST. If information on drug susceptibility for a specific drug was missing, then TB was assumed to be resistant to that specific drug.

In a sensitivity analysis, TB treatment regimens were considered "presumed active", where missing information on susceptibility for a specific drug was interpreted as the drug being susceptible.

For HCI components 1-7, each individual was classified as having the component or not (yes/no), and for components 8 and 9, the variables were the total number: categorized into ≥4, <4 prescribed TB drugs, and ≥3, <3 "known active" TB drugs, respectively. We could only identify "known active" drugs among individuals with a DST, so in multivariable statistical models, these two variables were fitted as an interaction, with no DST and no "known active" drugs as the reference category.

Statistical analysis

Individuals were divided into three geographical regions according to their country of residence: Eastern Europe (n=825; Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Russia, Ukraine), Western Europe (n=317; Belgium, Denmark, France, Italy, Spain, Switzerland, United Kingdom) and Latin America (n=254; Argentina, Chile, Mexico). Descriptive statistics of total numbers and percentages for categorical variables and median and interquartile ranges for continuous variables were used to compare baseline patient characteristic and potential HCI components across geographical regions. A two-tailed Chi-squared test was used to compare categorical variables .

The primary outcome was all-cause mortality. Individuals were censored at 12 months after TB diagnosis, date of death or loss to follow-up, whichever occurred first.

We evaluated the components of the previous HCI (DST preformed, initial TB treatment with RHZ and cART initiated within one month of TB diagnosis) using Cox proportional hazards models based on time from TB diagnosis to death, as previously described[1]. We additionally calculated the C-statistic using current data to assess model fit and to use as a comparison measure for expanded models incorporating the four additional measures of health care engagement.

To develop the HCI score, we assessed all nine potential HCI components outlined in the methods in a univariable Cox proportional hazards model on time from TB diagnosis to 12-month mortality. All variables that were statistically significant in univariable analysis: $p<0.10$, were included in a multivariable Cox proportional hazards model. Subsequently, factors in multivariable models with $p>0.10$ were removed and factors not previously included with $p>0.10$ were each added in turn one at a time, to assess whether their inclusion improved model fit. We also assessed model fit using the C-statistic.

Using the best fitting multivariable Cox proportional hazards model, coefficients were scaled by dividing by the smallest coefficient and rounding to the nearest whole number, as done previously[14]. The smallest coefficient was a negative number, so in order to make a higher HCI score indicative of better engagement in health care, we multiplied the scores by negative one. A HCI score was calculated for each individual based on their recorded health care factors and the health care factor weighting. The score was broken into four quartiles; the first quartile representing individuals with the lowest engagement in care, and the last quartile representing those with the highest engagement in care.

Kaplan-Meier methods were used to estimate the probability of death within 12 months of TB diagnosis, stratified by HCI quartile. Cox proportional hazards model were used to assess the association between HCI and time from TB diagnosis to 12-month mortality. We adjusted for patient characteristics that are known to be associated with mortality among TB-HIV positive individuals including, region of care, sex, CD4 cell count at TB diagnosis, previous AIDS diagnosis, previous TB diagnosis, presence of mycobacterial strains resistant to at least a rifamycin, and site of TB (pulmonary, extra-pulmonary, disseminated)[1]. In a sensitivity analysis, we examined the utility of the HCI score among those in Eastern Europe, among

injection drug users, and only using TB/HIV/AIDS related deaths within 12 months as the outcome.

Analyses were performed using STATA version 13.1.

Results

Baseline Characteristics

A total of 1396 individuals were eligible for this analysis and were predominately male (72%), with a majority from Eastern Europe (59%). In Eastern Europe, there was a higher proportion of injection drug users (p<0.001) and of individuals who were Hepatitis C antibody positive (p<0.001), Table 1. Across all regions, CD4 cell counts were low (median (interquartile range:IQR) 110 (36 to 273) cells/mm) and HIV-RNA high (5.1 (3.4 to 5.7) $\log_{10}$ copies/ml). Overall, 70% were diagnosed with HIV more than three months prior to TB diagnosis; 899 (64%) were cART naïve when diagnosed with TB, and this proportion was higher in Eastern Europe (75%) compared to Southern and Western Europe (49%), and Latin America (49%), p <0.001.

Components of the Health Care Index

DST was performed for 41% of individuals, but in Western Europe a higher proportion (64%) had a DST compared with Eastern Europe (36%) and Latin America (33%), p <0.001. Initial TB treatment contained RHZ in the majority of individuals (84%) which was similar across regions. A higher proportion of individuals had a CD4 cell count and HIV-RNA assessment before/soon after TB diagnosis in Western Europe (96% and 92%, respectively) compared with Eastern Europe (78% and 49%, respectively) and Latin America (86% and 63%, respectively), p<0.001 for both HIV-RNA and CD4 cell counts. Eastern Europe had the lowest proportion of individuals starting cART before/soon after TB diagnosis (18%) compared with Western Europe (44%), and Latin America (40%), p<0.001.

Univariable analysis showed DST, RHZ-based TB treatment, the number of active and presumed-active TB drugs, having a CD4 and HIV-RNA measurement done before/just after TB diagnosis, and initiating cART before/soon after TB diagnosis were associated with a reduced risk of death within 12 months of TB diagnosis, Table 2. In multivariable analysis, RHZ-based TB treatment, DST and the number of known active drugs, HIV-RNA measurement and cART initiation remained significantly associated with reduced mortality at 12-months.

These factors were then included in the final HCI model. The C-statistic for the final model was 0.62 (0.58 to 0.65). In a sensitivity analysis, where missing information on susceptibility for a specific drug was interpreted as the drug being 'presumed active', we found similar results to the main analysis (data not shown).

When validating the previously published HCI model[1] we found similar results for key variables and model fit in the present study. Initiating a TB regimen containing RHZ was associated with a reduced risk of death at 12 months; adjusted HR (aHR) =0.67 (95% Confidence Interval (CI) 0.50 to 0.89) compared with 0.43 (95% CI 0.31 to 0.58) derived from the previous model. This was also true for cART aHR =0.72 (95% CI 0.53 to 0.97) compared with 0.36 (0.24 to 0.55). In our present model, we additionally identified that a recent HIV-RNA measurement and the number of active drugs prescribed among those who had DST results were important prognostic health care indicators, which is supported by the higher C-statistic than the one derived from using covariates in the previous HCI model; C-statistic =0.62 ((95% CI 0.58 to 0.65) compared with 0.59 (95% CI 0.55 to 0.62), respectively, thus demonstrating a modest improvement.

Using the coefficients (the natural logarithm of the hazard ratios) of our final model, we used DST with fewer than three active drugs in the initial TB regimen to scale all other coefficients, as this was the closest coefficient to zero. Scaling the coefficients yielded individuals to receive five points for each RHZ and HIV-RNA, four points for cARTsaa, eight points for DST with at least three active TB drugs in the initial TB regimen, and negative one point for DST and fewer than three active TB drugs in the initial regimen, Table 2.

Overall, scores thus ranged from -1 to 22, with higher scores indicative of better utilisation of health care. The HCI score was divided into four quartiles namely: -1 to 5 =very low utilisation, 6 to 10 =low, 11 to 14 =intermediate, and 15 to 22 =high utilisation. The HCI score was then calculated for each patient.

A majority of individuals (73%) in Western Europe had intermediate to high HCI scores, whereas only 26% of individuals in Eastern Europe had an intermediate to high HCI. The highest proportions of individuals with a very low HCI were in Eastern Europe (43%) and Latin America (25%), compared with 3% in Western Europe, Figure 1.

We further investigated HCI distribution within individual countries and found consistently high HCI in Western Europe; less than 5% of individuals in any Western European country had very low HCI scores. By contrast, across Eastern European countries HCI scores were

consistently low, however there was slightly more variation, with patients with very low HCI scores ranging from 11% to 59% in the individual countries in Eastern Europe (data not shown).

Those with lower HCI scores had an increased probability of death. At 12 months those in the very low category had a 30% (95% CI 26% to 35%) probability of death and those with high HCI scores had a 9% probability of death (95% CI 6% to 13%) (Figure 2).

In a Cox proportional hazards model using time from TB diagnosis to death within 12 months, and including HCI in univariable analysis we found a 35% reduction in the HR of death per unit increase in HCI quartile (HR =0.65 (95% CI 0.58 to 0.74) C-statistic =0.61. The HCI score remained independently associated with 12-month mortality after adjusting for factors previously identified as being associated with mortality (aHR 0.86 (95% CI 0.74 to 0.99), C-statistic =0.74, (Table 3).

Sensitivity analysis showed results consistent with our main findings. When restricting analysis to Eastern Europe, in adjusted models we found a 15% reduction in the aHR of death per unit increase in HCI quartile (aHR =0.85 (95% CI 0.72 to1.01), C-statistic =0.69). When restricting analysis to include only injection drug users, a 25% reduction in the aHR of death per unit increase in HCI (aHR =0.75 (95% CI 0.63 to 0.90), C-statistic =0.70) was observed, and when investigating only deaths related to TB/HIV/AIDS, we found a 35% reduction in the HR of death per unit increase in HCI quartile (aHR =0.65 (95% CI 0.54 to 0.79), C-statistic =0.70). We also modelled the HCI score as a categorical variable, but found no evidence suggesting departures from linearity, likelihood ratio test p-value =0.64.

Discussion

In this study we investigated how utilisation of health care for HIV/TB coinfected patients affected their outcome. We found five main components of health care that were associated with a reduction in 12-month mortality among TB/HIV positive individuals; namely initiating RHZ-based TB treatment, performance of DST with inclusion of at least three active drugs in the initial TB treatment, having a baseline HIV-RNA measurement and provision of cART. This not only supports our previous model, but also expands it with the inclusion of number of active drugs and having a recent HIV-RNA measurement.

HCI reflects essential components of health care for TB/HIV coinfected individuals. In TB management, it is paramount that the diagnosis is well established (bacteriologically confirmed) and drug susceptibility patterns are identified. Implementation of rapid TB diagnostic tests, which can simultaneously identify resistance to the main TB drugs (rifamycins), has greatly reduced time to establishment of the diagnosis and assessment of resistance patterns which has enabled clinicians to promptly tailor treatments. This is particularly important in Eastern Europe where levels of MDR-TB are extremely high. For example, in Belarus, the prevalence of MDR-TB among new TB cases is approximately 30%, and among previously treated TB cases around 70%[15]. These patients are unlikely to benefit from starting treatment with a standard RHZ-based regimen, and should rather receive individualised treatment regimens based on the susceptibility patterns.

To design a HCI, we chose parameters that characterise utilization of health care rather than patients' characteristics. For example, having DST performed, rather than the outcome of the DST in having drug-resistant TB. Thus, our HCI permits assessment of how utilization of health care relates to patients' outcome. This assessment can be done on an individual level as well as at a cohort (e.g. clinic, country, etc) level, and could be a valuable tool in predicting patients' prognosis, as well as evaluating the health care provided. Further, based on data-driven identification of health care factors associated with better outcomes, and level of utilization of these factors, a benchmark for HIV/TB coinfection care can be established. Such a benchmark is needed in order to identify gaps in healthcare systems, as we have done previously[16], and to develop specific strategies for improvement. In our study, we have identified disparities in health care utility, where, on average, individuals in Eastern Europe and Latin America have much lower HCI than those in Western Europe. More widespread use

of available diagnostic tools and appropriate therapeutic interventions might result in improved patient outcomes.

RHZ-based treatment remained a significant component of our HCI and is associated with reductions in 12-month mortality. This is unsurprising, as it is the recommended treatment for drug sensitive TB, which was present in the majority of patients enrolled in the study. Previous reports have shown the number of active drugs predicts mortality[5,17], so we incorporated this as a new HCI component to reflect adequate initial management of MDR-TB. This became the strongest component of our HCI which was assigned eight points (vs. <5 for all other variables) highlighting the importance of personalized treatment for drug resistant TB. Although treatment for MDR-TB should follow the latest WHO guidelines and where available be based on DST results, we found no major differences between the number of known active and presumed active drugs.

Overall, in our cohort, 9% of individuals were known to have MDR- TB, which was substantially higher in Eastern Europe, where 22% of all individuals were known to have MDR TB[5,13]. This significance of the 'drug activity' variable may reflect a growing personalised approach to tailoring TB treatment based on results of rapid genotypic DST combined with better access to a variety of both old and newer TB drugs.

In our primarily European setting, use of co-trimoxazole was not associated with death in univariate models, which is in contrast to previous reports from African cohorts[9,10]. The lack of association does not seem to be due to lack of power as approximately 35% of our population received co-trimoxazole, but it may be due to different patient populations studied.

A large component of healthcare provision to individuals with HIV/TB is appropriate HIV management which includes cART, and immunological and virological monitoring. Since 2010, the WHO recommend that all HIV-positive individuals diagnosed with TB should initiate cART as soon as possible irrespective of their CD4 cell counts[7,18]. In our study, only 28% of individuals were prescribed cART before or up to a month after TB diagnosis, and notably, this was lowest in Eastern Europe (18%). It may be that clinicians during the recruitment period for the present study (2009-2011) only slowly implemented earlier initiation of ART in TB-coinfected patients in clinical practice. As expected, a large proportion of our population were monitored with 84% of individuals having a recent CD4 cell count measurement, and 61% having a recent HIV-RNA measurement. Among those taking or initiating cART, the

percentages of individuals monitored increased, where 90% had a CD4 cell count measurement and 77% had an HIV-RNA measurement. HIV-RNA and cART, not CD4, became components of our HCI which could reflect the importance of HIV-RNA monitoring and viral suppression among those on cART as a marker of good management of HIV infection in the test and treat era.

The C-statistic in our HCI model was 0.62, which is a modest improvement from the previous HCI model with a C-statistic of 0.59. Although this is considered low[19], the purpose of our model was not to capture complete prediction, but rather to focus on health care. Unsurprisingly, when adjusted for factors known to be associated with death in our model, the C-statistic increased to 0.74. Even so, after adjusting for these factors, our HCI score remained statistically significant, suggesting it is a valuable tool with the potential to guide improved health care engagement. The HCI can be used at an individual or population level, and as a tool for clinicians to assess appropriate interventions to achieve good outcomes and in settings where healthcare needs improvement, for example, where cART or DST is limited, or where HIV-RNA is not routinely measured.

Some limitations of our study should be noted. As with all observational studies, the validity of our estimates relies on the untestable assumption that we have appropriately adjusted for confounding. If there were other unmeasured factors that predict mortality, it is possible that after these adjustments, our HCI score does not have the same utility. However, we adjusted for factors that are known to be associated with short term mortality among TB/HIV positive individuals. Our model relates to individuals in Europe and Latin America, but a logical next step would be to validate this in other TB/HIV co-infected populations.

In conclusion, we have improved our previous HCI, reflecting recent changes in health care practices, which predicts 12 month-mortality, even after adjusting for factors known to be associated with mortality among TB/HIV positive individuals. Our HCI has value in both high and low income settings in Western and Eastern Europe, as well as Latin America. Our model suggests that five simple factors can be used to improve mortality among TB/HIV positive individuals and can be used for benchmarking clinics and serve as a guide to improve health care provision to people with HIV/TB.

Table 1: Baseline* Characteristics and potential health care index components in TB-HIV patients stratified by geographic region.

	Eastern Europe n = 825		Western Europe n = 317		Latin Am n = 25
	n	%	n	%	n
Patient characteristics					
Male sex	618	75	204	64	18
IDU (as risk factor for TB)‡	560	69	64	21	4
Hepatitis C antibody-positive‡	435	75	60	26	2
Disseminated TB ʅ	484	59	165	52	11
Rifamycin-resistant TB ¥	111	40	9	5	1
Prior AIDS	188	23	85	27	11
Age, years, median [IQR]	35 (31, 40)		40 (33, 48)		39
CD4 cell count, cells/µl, median [IQR] λ	102 (35, 246)		138 (40, 339)		101 (
HIV-RNA, log10 copies/ml, median [IQR] ξ	5.2 (4.4, 5.7)		4.8 (2.3, 5.6)		4.7 (
cART naïve at TB diagnosis	621	75	154	49	12
HIV diagnosis > 3 months prior to TB diagnosis	628	76	187	59	16
Potential Health Care Index components					
Definite TB diagnosis γ	456	55	232	73	14
Co-trimoxazole prophylaxis δ	298	36	116	37	7
DST performed	296	36	204	64	8
RHZ-containing TB treatment	658	80	289	91	23
# TB drugs prescribed, median [IQR] Ł	4 (4, 5)		4 (4, 4)		4 (4,
<4, ≥4 perscribed TB drugs	784	95	294	93	24
<3, ≥3 known active TB drugs	147	18	183	57	3
CD4 cell count measurement ŋ	644	78	303	96	21
HIV-RNA measurement ŋ	403	49	290	92	15
cART initiated Ł	150	18	140	44	10

* Baseline defined as the date of TB diagnosis.

IDU =injection drug use; cART =combination antiretroviral therapy; DST = drug susceptibility testing

ſ Western Europe: Belgium, Denmark, France, Italy, Spain, Switzerland, United Kingdom; Eastern Europe: Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Russia, Ukraine; Latin America: Argentina, Mexico, Chile

‡ TB risk was unknown for 24 individuals, 6 (25%), 14 (58%), 4 (17%) from Western Europe, Eastern Europe and Latin America, respectively.

ǂ Hep C was unknown for 416 individuals, 86 (21%), 245 (59%) 85 (20%) from Western Europe, Eastern Europe and Latin America, respectively.

ʅ TB involving more than one organ system, miliary TB or *Mycobacterium tuberculosis* isolated from blood or bone marrow.

¥ Proportion of those with DST preformed

λ Baseline CD4 unknown for 167 individuals, 9 (5%) 135 (81%), 23 (14%), from Western Europe, Eastern Europe and Latin America, respectively.

ξ Baseline HIV-RNA unknown for 449 individuals, 16 (4%), 373 (83%), 60 (13%) from Western Europe, Eastern Europe and Latin America, respectively.

γ World Health Organization (WHO) defined definite diagnosis of TB: culture-confirmed disease due to M. tuberculosis and/or at least one sputum smear examination positive for acid-fast bacilli (AFB)
δ Any co-trimoxazole treatment prescribed within one month of TB diagnosis excluding individuals with PCP or Toxoplasmosis diagnoses any time before TB diagnosis.
ł before or within one month of TB diagnosis
ŋ preformed 6 months before and up to one month after TB diagnosis.

Table 2: Results from Cox proportional Hazards model on time from TB diagnosis to 12-month mortality and calculation of the HCI using the TB:HIV dataset.

	Univariable			Multivariable			Final				
Model Components	**HR**	**95 % CI**	**p**	**HR**	**95 % CI**	**p**	**HR**	**95 % CI**	**p**	**Ln HR**	**HCI**
Definite TB diagnosis	1.02	(0.80, 1.30)	0.892								
Co-trimoxazole prophylaxis τ	1.21	(0.95, 1.55)	0.126								
RHZ-containing treatment	0.58	(0.43, 0.77)	0.000	0.67	(0.50, 0.89)	0.007	0.67	(0.50, 0.89)	0.007	-0.40	5
DST preformed	0.67	(0.52, 0.87)	0.002	-			-				
DST & <3 known active TB drugs prescribed δ vs. no DSTα	-			1.09	(0.80, 1.48)	0.586	1.09	(0.80, 1.48)	0.594	0.08	-1
DST & ≥3 known active TB drugs prescribed δ vs. no DSTα	-			0.49	(0.35, 0.70)	0.000	0.49	(0.35, 0.70)	0.000	-0.70	8
# known active TB drugs prescribed δλ	0.78	(0.71, 0.85)	0.000	-			-				
≥3 known active TB drugs prescribed δ¥	0.44	(0.32, 0.62)	0.000	-			-				
# TB drugs prescribed δ λ	1.08	(0.97, 1.21)	0.168								
≥4 TB drugs prescribed δ	1.00	(0.58, 1.71)	0.994								
CD4 cell count measurement ł	0.68	(0.51, 0.91)	0.010	0.94	(0.67, 1.30)	0.700					
HIV-RNA measurement ł	0.56	(0.44, 0.71)	0.000	0.66	(0.50, 0.87)	0.004	0.64	(0.50, 0.82)	0.000	-0.44	5
cART initiated γ	0.65	(0.49, 0.87)	0.004	0.72	(0.53, 0.97)	0.029	0.72	(0.53, 0.97)	0.028	-0.33	4
c-stat (95 % CI)				0.62	(0.59 0.66)		0.62	(0.58, 0.65)			

τ up to 1 month before or 1 month after TB diagnosis (not for PCP or Toxoplasmosis diagnosed any time before TB)

α variable only included in multivariable models due to co-linearity between DST and the number of active drugs, as we were only able to assess the number of active TB drugs within a regimen only among individuals with a DST. For this same reason, DST and number of known active drugs were not included together in multivariable models.

δ up to 1 month before or 1 month after TB diagnosis

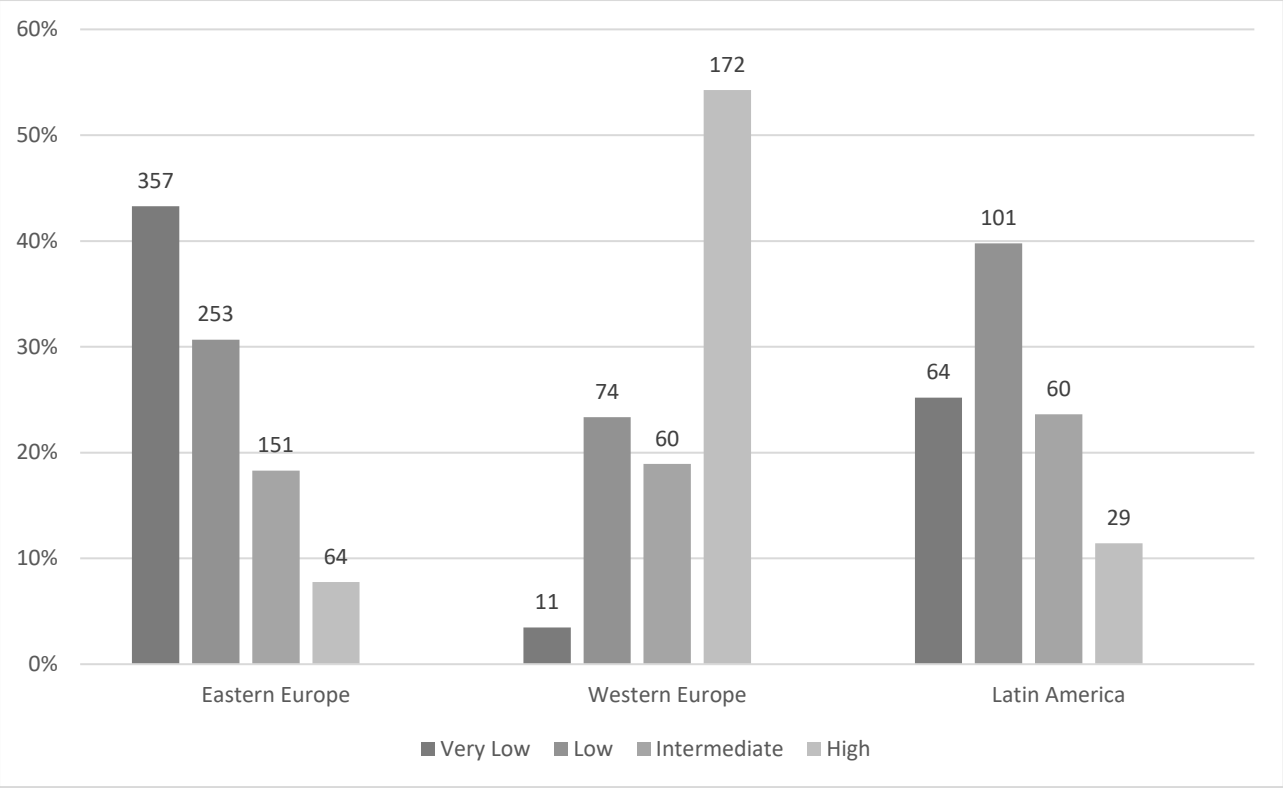
λ per drug increase

¥ only included in univariable models due to co-linearity between DST and the number of active drugs

ł performed from 6 months before to 1 month after TB diagnosis

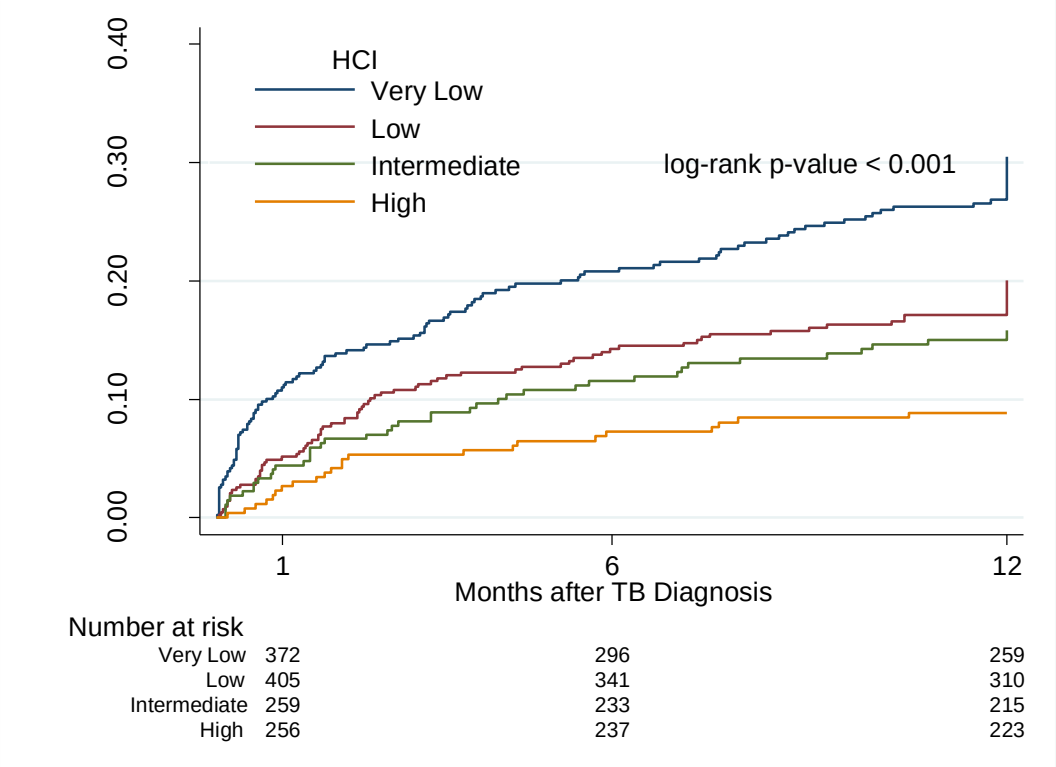
γ cART initiated any time before or up to 1 month after TB diagnosis

Figure 1: Distribution of patients according to HCI quartile and region of residence using the TB:HIV dataset.



Numbers above the bars are total number of individuals in each HCI quartile per region, Chi-squared p <0.001
HCI: -1 to 5 = very low, 6 to 10 = low, 11 to 14 = intermediate, and 15 to 22 = high

Figure 2: Kaplan Meier estimates for probability of death after TB diagnosis according to HCI quartile using the TB:HIV dataset.



HCI scores: -1 to 5 = very low, 6 to 10 = low, 11 to 14 = intermediate, and 15 to 22 = high.

Table 3: Univariable and Multivariable hazard ratios for time from TB diagnosis to 12 month mortality adjusting for other factors known to be associated with mortality among TB and HIV co-infected individuals using the TB:HIV dataset.

	Univariable					Multivariable									
						With HCI Score					Without HCI score‡				
	HR	**95 % CI**		**p**	**c-stat**	**HR**	**95 % CI**		**p**	**c-stat**	**HR**	**95 % CI**		**p**	**c-stat**
HCI quartile as a continuous variable	0.65	0.58	0.74	< 0.001	0.61	0.86	0.74	0.99	0.040	0.74					
Region															
Eastern Europe	1.00	1.00			0.67	1.00					1.00				0.74
Southern/Western Europe	0.13	0.07	0.22	< 0.001		0.19	0.10	0.34	< 0.001		0.15	0.09	0.3	< 0.001	
Latin America	0.39	0.27	0.56	< 0.001		0.37	0.24	0.57	< 0.001		0.35	0.23	0.5	< 0.001	
Sensitivity Analyses															
Eastern Europe (n = 825, deaths = 225)	0.78	0.67	0.91	< 0.001	0.61	0.85	0.72	1.01	0.058	0.69					
Injection Drug Users (n = 614, deaths = 154)	0.74	0.62	0.87	< 0.001	0.61	0.75	0.63	0.90	< 0.001	0.70					
TB/HIV/AIDS deaths (deaths = 140)	0.61	0.51	0.73	< 0.001	0.61	0.65	0.54	0.79	< 0.001	0.70					
HCI category as categorical variable															
Very Low	1.00	1.00			0.61	1.00				0.71					
Low	0.62	0.47	0.82	0.026		0.72	0.53	0.99	0.044						
Intermediate	0.48	0.34	0.68	< 0.001		0.60	0.40	0.90	0.013						
High	0.26	0.17	0.40	< 0.001		0.27	0.17	0.44	< 0.001						

Multivariable model adjusted for sex, CD4 cell count at TB diagnosis (≥, < 200 cells/mm^3), previous AIDS diagnosis, previous TB diagnosis, presence of *Mycobacterium tuberculosis* strains with resistance to at least a rifamycin, and site of TB (pulmonary, extra-pulmonary, disseminated).

‡Adjusted for all covariates in the multivariable model ,apart from HCI score

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