TB:HIV an international prospective observational study

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Excess TB Mortality in HIV Patients in Eastern Europe

Restructured Approach to Care Needed

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on behalf of the TB:HIV study group in EuroCoord

UCL chip REGION H Rigshospitalet SEVENTH FRAMEWORK PROGRAMME EuroCoord

Disclosure

- I have no conflicts of interest to disclose

Background

- Tuberculosis (TB) is a leading cause of HIV-related mortality and morbidity world-wide[1]
- Managing TB and HIV co-infection is complicated by:
  - Frequent extrapulmonary and disseminated disease[2]
  - Drug interactions and overlapping toxicities[2]
- Eastern Europe:
  - High prevalence of multidrug-resistant (MDR) TB (>15%)[3]
  - 2004-2006: Mortality rates 3-5 times higher than in Western Europe[4]
  - Lack of drug susceptibility testing (DST) and initial TB treatment regimens with limited activity common[5]

1. WHO, 2014 ; 2. Havlir, JAMA, 2008; 3. WHO regional office, 2015; 4. Podlekareva, 2009; 5. Efsen 2014

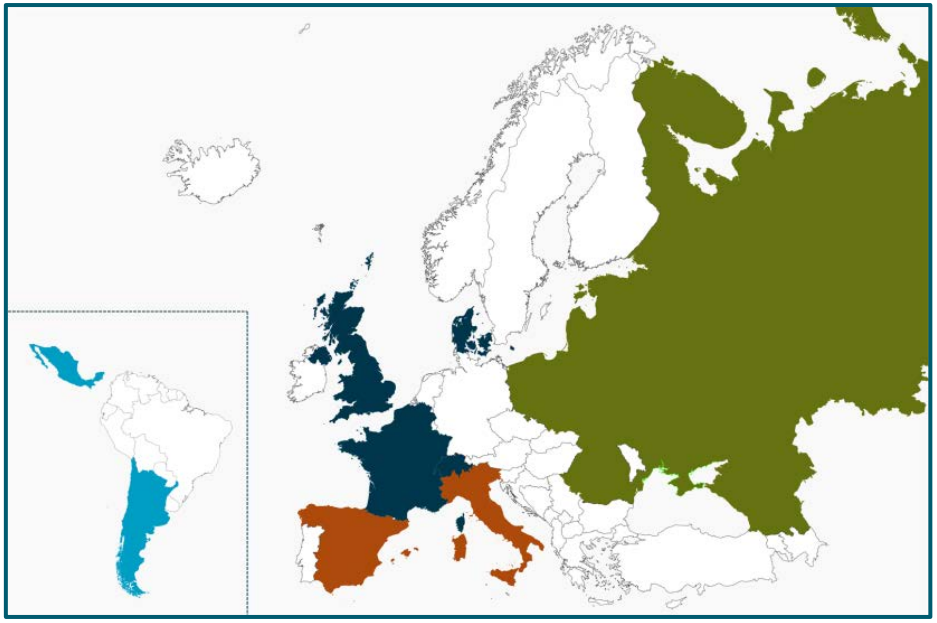
Aims

- Estimate TB mortality at one year after TB diagnosis in Eastern Europe (EE) compared with Western and Southern Europe (WSE), and Latin America (LA)
- Determine factors associated with one-year mortality from TB, in particular influence of:
  - Number of active anti-TB drugs used in the initial treatment

TB:HIV study

- Prospective cohort of TB/HIV co-infected patients
- Inclusion criteria:
  - HIV positive
  - Diagnosed with TB between 2011 – 2013
  - > 16 years of age

TB:HIV study



- **Eastern Europe**: 21 clinics in Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine and Russia — **EE**
- **Western Europe**: 19 clinics in Belgium, Denmark, France, Switzerland and the United Kingdom — **WSE**
- **Southern Europe**: 9 clinics in Italy and Spain — **WSE**
- **Latin America**: 13 clinics in Argentina, Chile and Mexico — **LA**

Methods – Key Definitions

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- **Baseline Drug Susceptibility Testing (DST):** Mycobacterium tuberculosis sample taken +/- 4 weeks of starting TB treatment
- **Number of active drugs:** Number of drugs in the initial regimen to which no resistance was consequently reported
  - Given that a DST was done, an individual was presumed to be susceptible to those drugs with a missing DST result
  - Sensitvity analysis: Required an individual to have DST data on all drugs used as part of the initial regimen

Methods - Statistics

- Causes of death were established using CoDe methodology[1]
- Standard survival methods (KM plots, Cox models) used to assess the risk of TB death
- Individuals censored at their last clinic visit, date of death from non-TB or 12 months after baseline, whichever occured first

1. Kowalska, Epidemiology, 2011

Baseline Characteristics (N=1406)

		EE N=834 (59%)	WSE N=317 (23%)	LA N=255 (18%)	
		N *(%)*	N *(%)*	N *(%)*	*P*
Gender	Male	626 *(75)*	204 *(64)*	186 *(73)*	0.001
Hepatitis C	HCV Ab positive	433 *(52)*	61 *(19)*	27 *(11)*	<0.001
IDU	Ever IDU	565 *(68)*	65 *(21)*	46 *(18)*	<0.001
HIV treatment	On cART[1]	152 *(18)*	138 *(44)*	99 *(39)*	<0.001
TB Type	Disseminated	485 *(58)*	161 *(51)*	118 *(47)*	<0.001
Diagnosis	Definite[2]	327 *(45)*	220 *(69)*	94 *(37)*	<0.001
Treatment	RHZ based[3]	636 *(76.3)*	286 *(90.2)*	230 *(90.2)*	<0.001
		Median *[IQR]*	Median *[IQR]*	Median *[IQR]*	*P*
Age	Years	35 *(31-40)*	40 *(33-48)*	39 *(30-45)*	<0.001
HIV disease	CD4 count	103 *(35-247)*	136 *(38-240)*	101 *(36-287)*	0.03
	RNA (log)	5.2 *(4.4-5.7)*	4.8 *(2.3-5.6)*	4.7 *(1.9-5.5)*	<0.001

1. cART=on at least 3 HIV drugs at diagnosis, 2. Definite=Culture or PCR confirmed,
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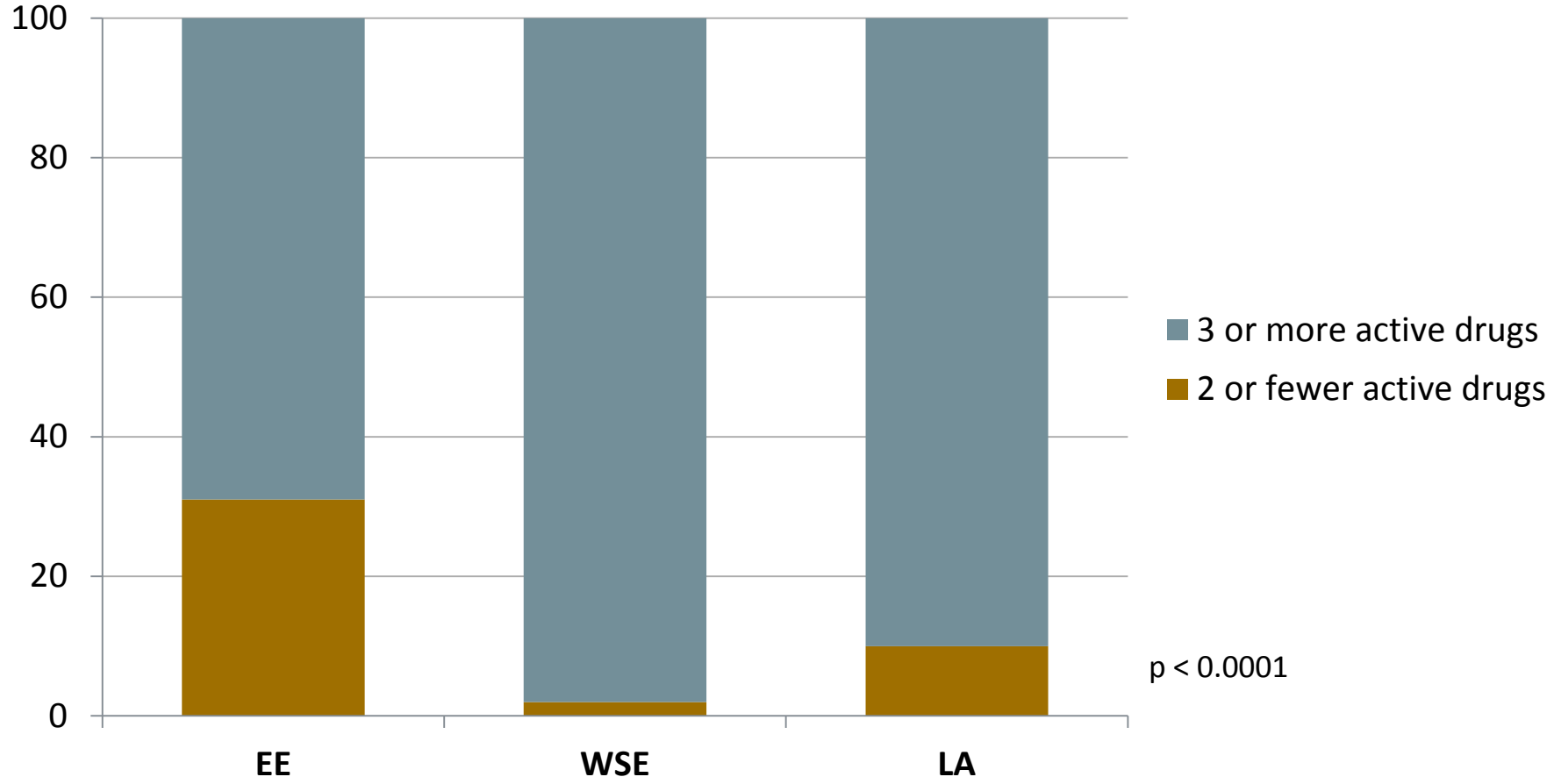
Number of active drugs in the initial regimen

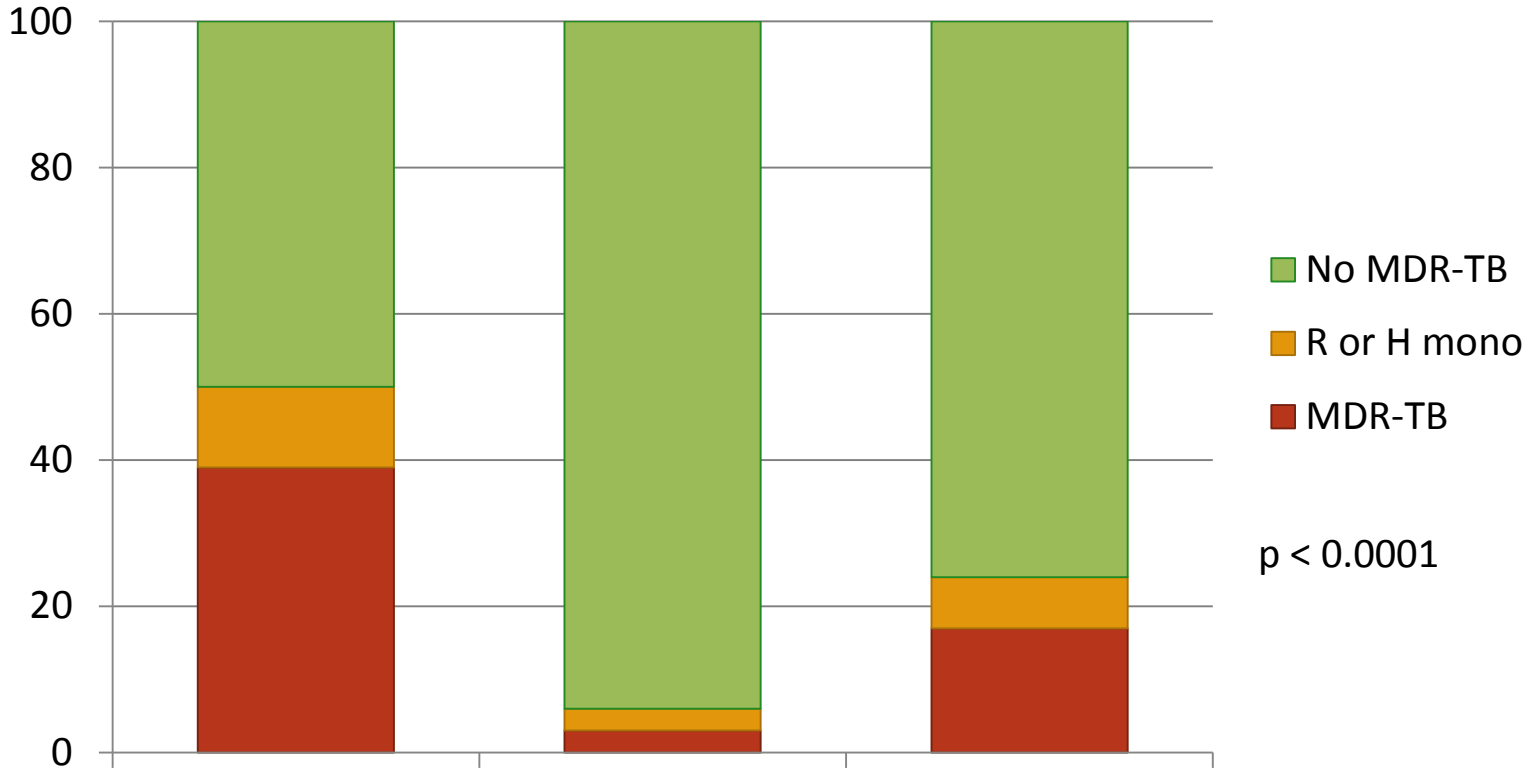
- **576** (41%) had baseline DST performed



	EE	WSE	LA
3 or more N(%)	201 (69)	197 (98)	90 (75)
2 or fewer N(%)	90 (31)	5 (2)	8 (10)

MDR[1] prevalence among those tested for MDR

- **576** had baseline DST performed
  - **495** (86%) had data on both R and H resistance

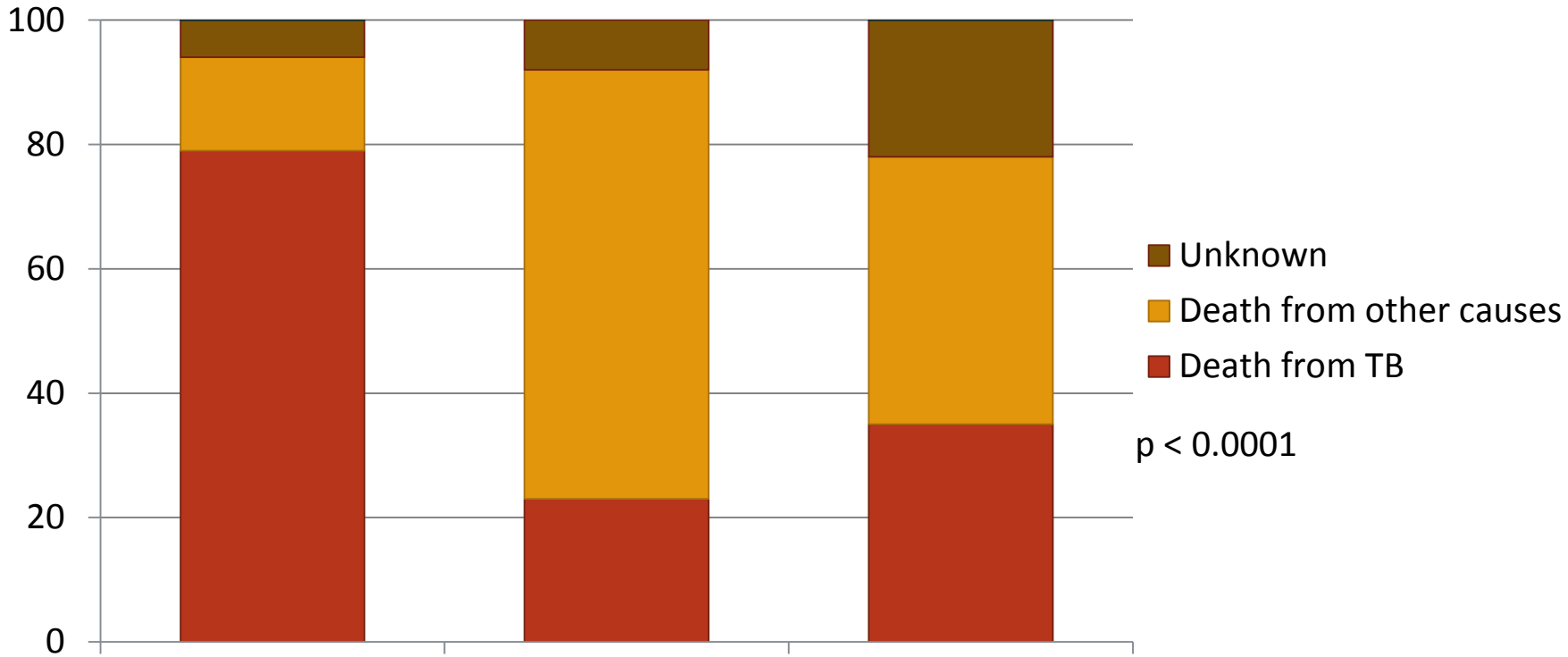


	EE	WSE	LA
No MDR-TB N (%)	126 (50)	124 (94)	49 (17)
R or H mono N (%)	29 (11)	6 (3)	5 (7)
MDR-TB N (%)	99 (39)	6 (3)	11 (17)

1. MDR=Resistance to R and H

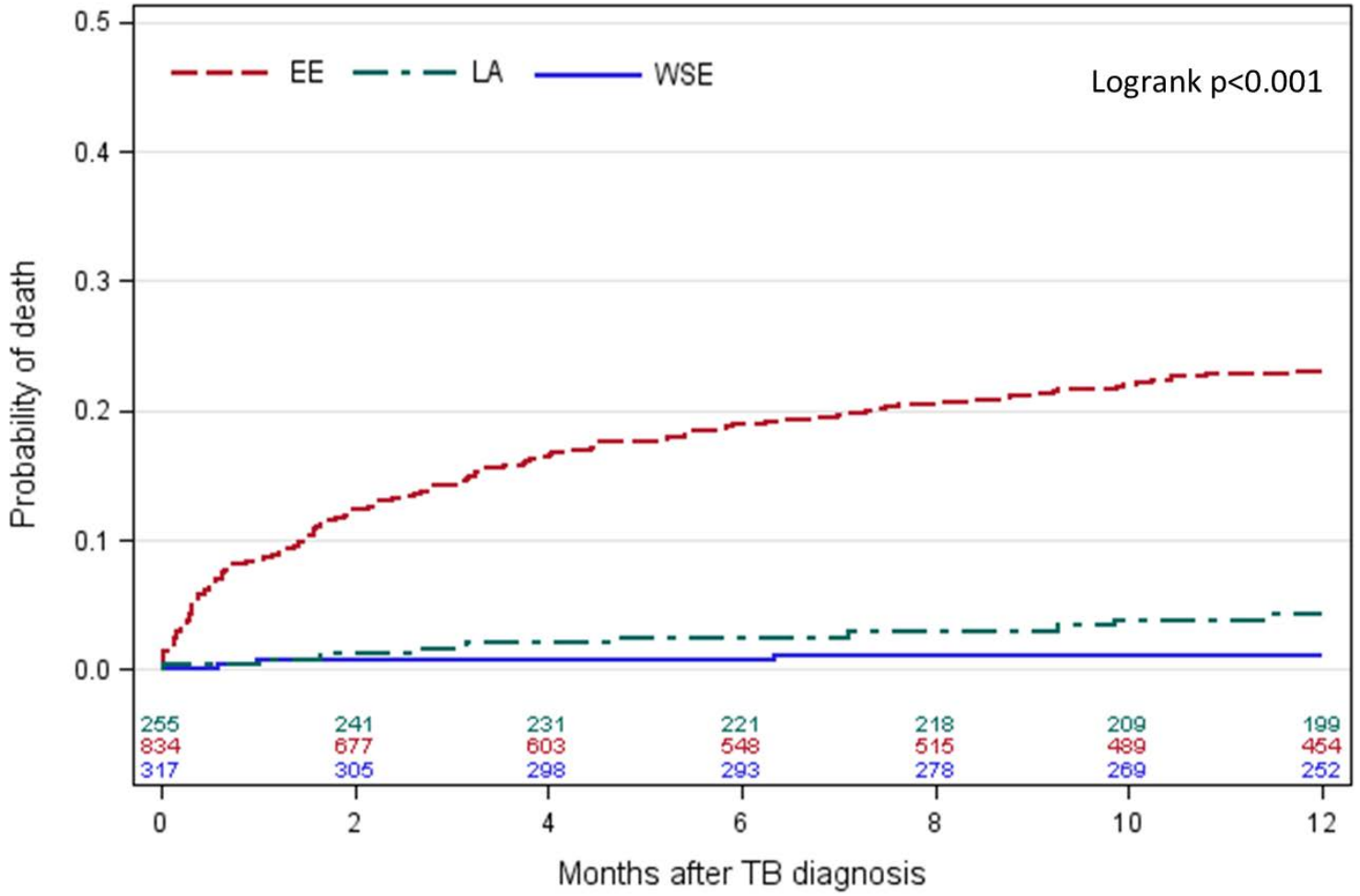
Overall Mortality and Causes of Death

- **265** individuals (19%) died within 12 months
  - **188** (71%) of these deaths could be classified as TB-related

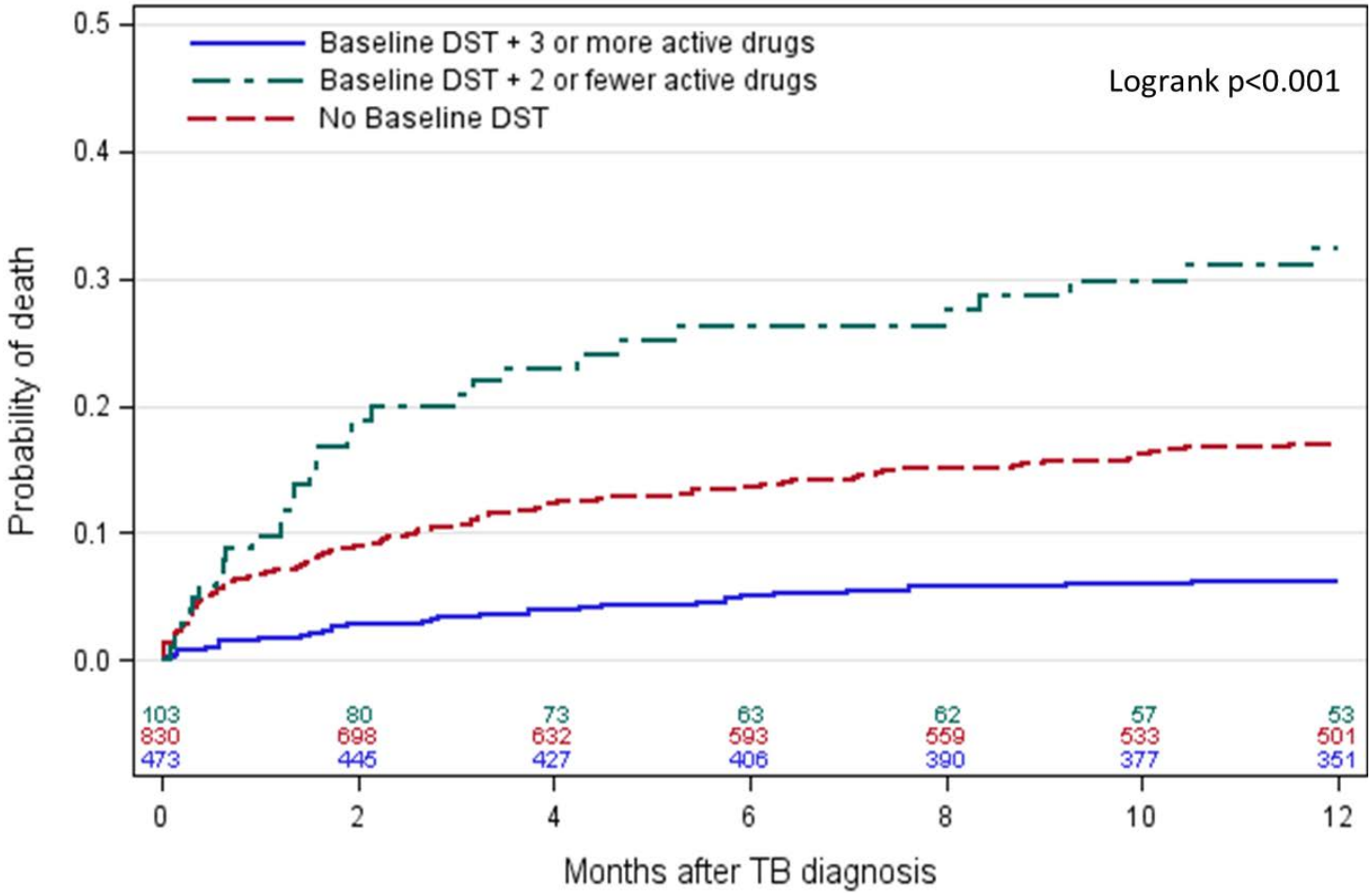


	EE	WSE	LA
TB N(%)	175 (79)	3 (23)	10 (36)
Other N(%)	34 (15)	9 (69)	12 (43)
Unknown N(%)	14 (6)	1 (8)	6 (21)

Probability of TB death, according to geographical region

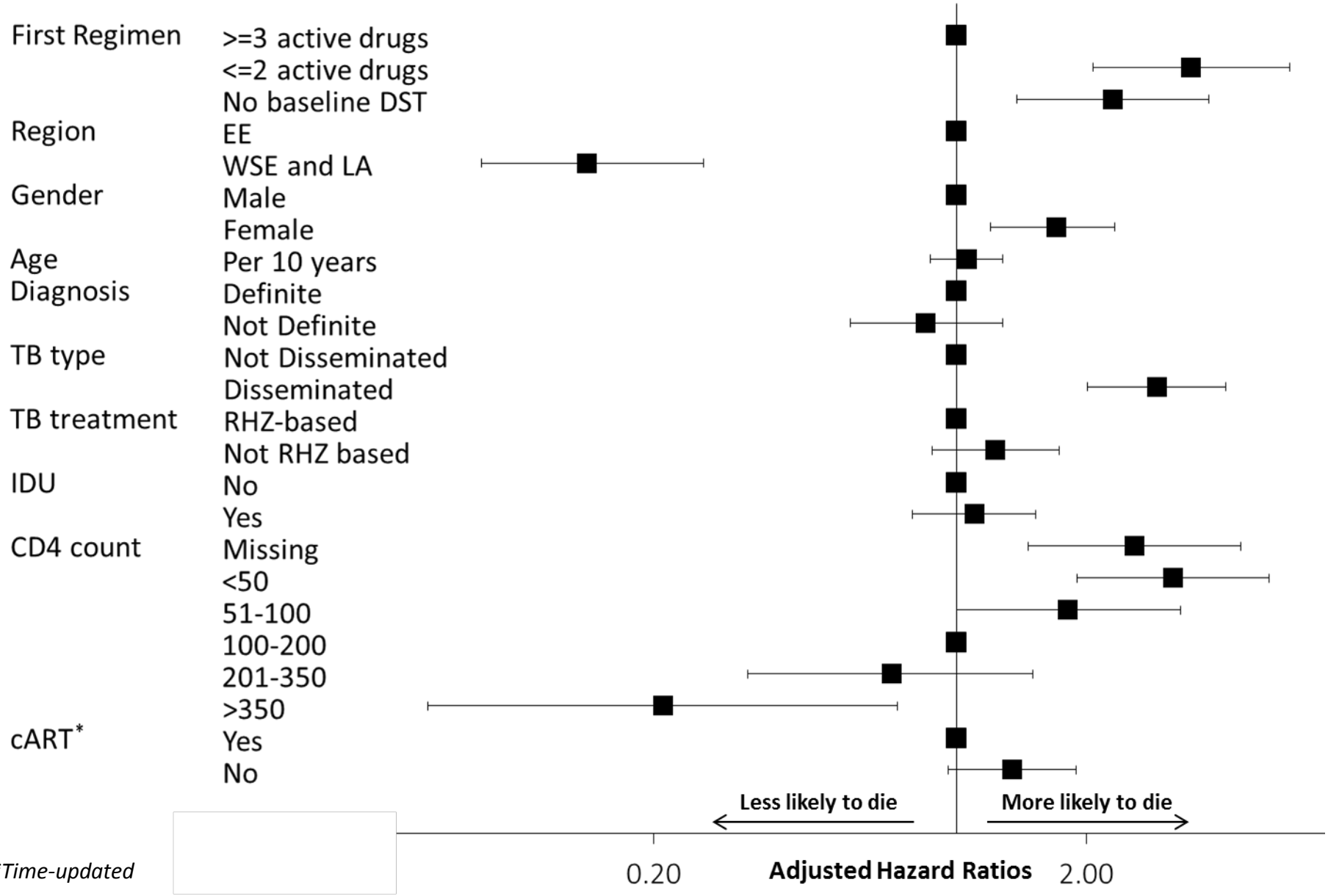


Probability of TB death, according to number of active drugs in the initial regimen



**Sensitivity analyses were highly consistent with these results*

Factors Associated with TB death



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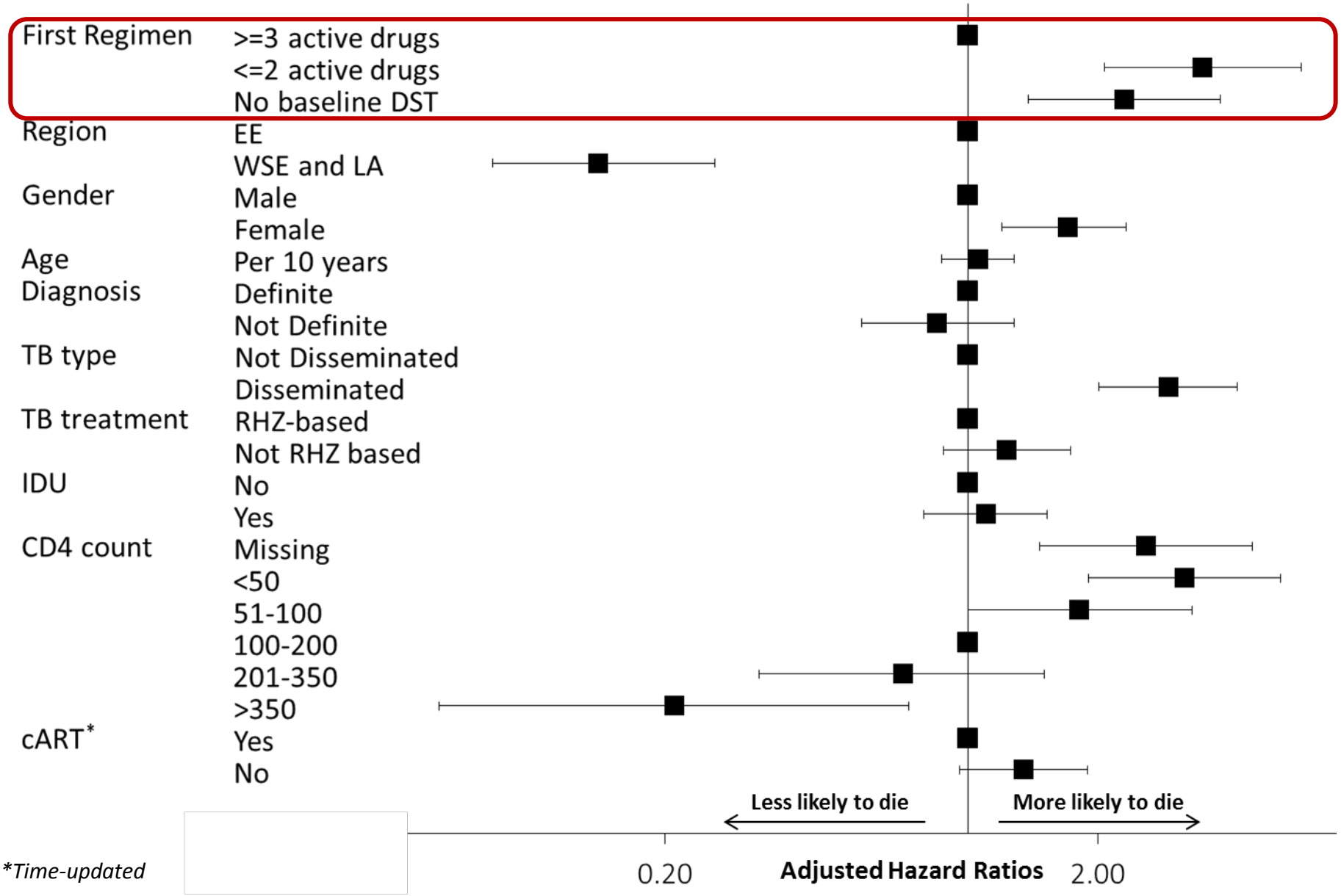

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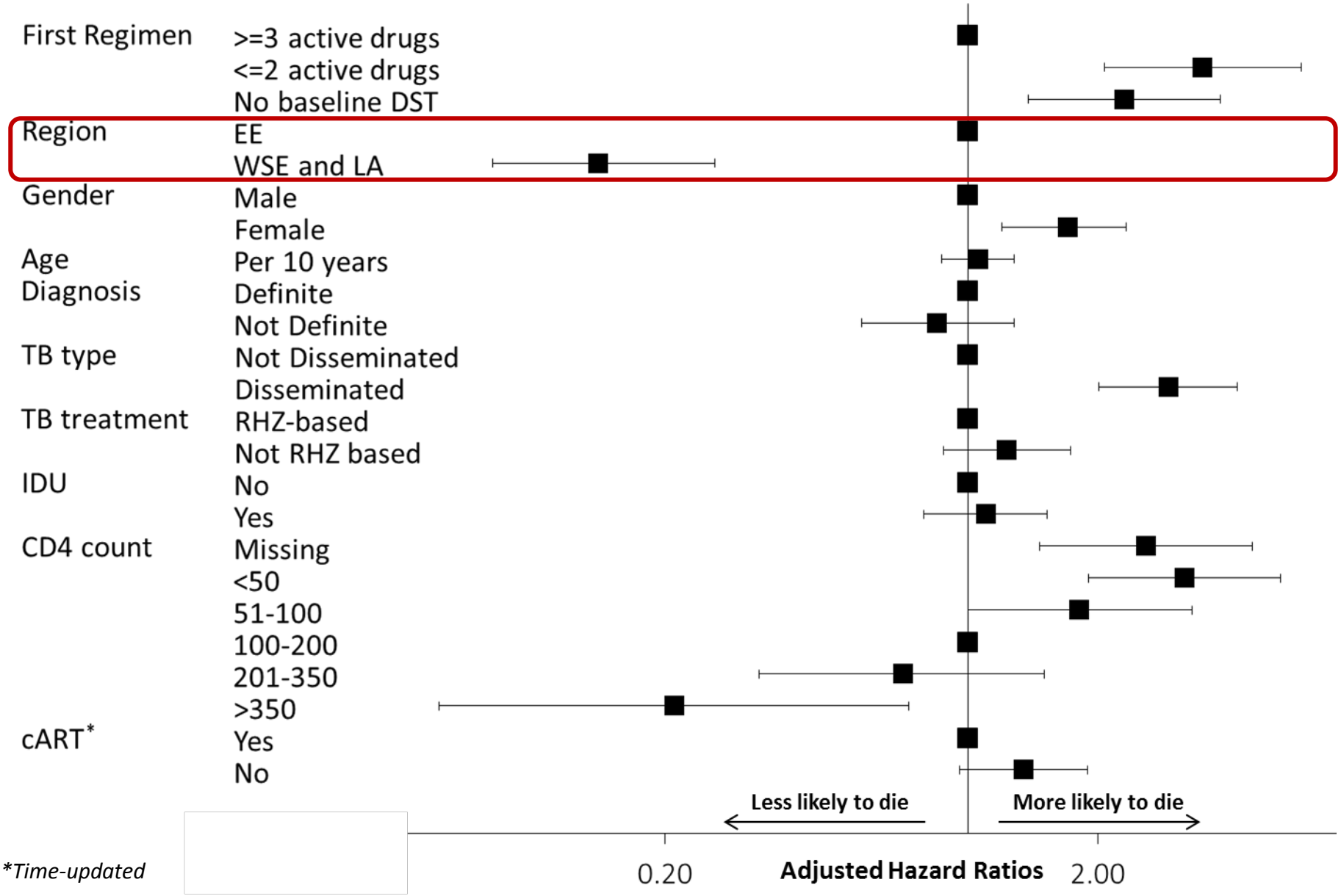

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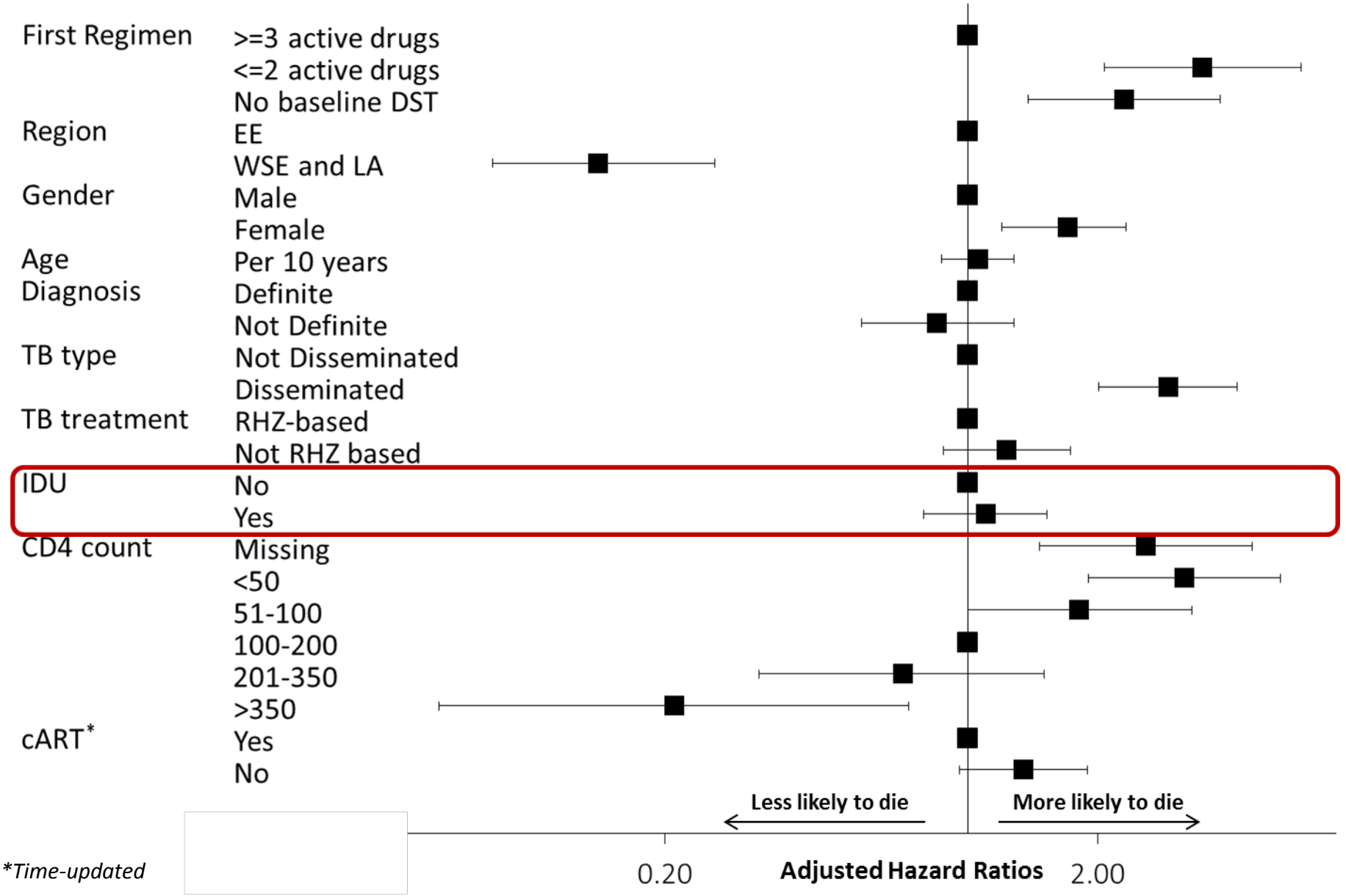

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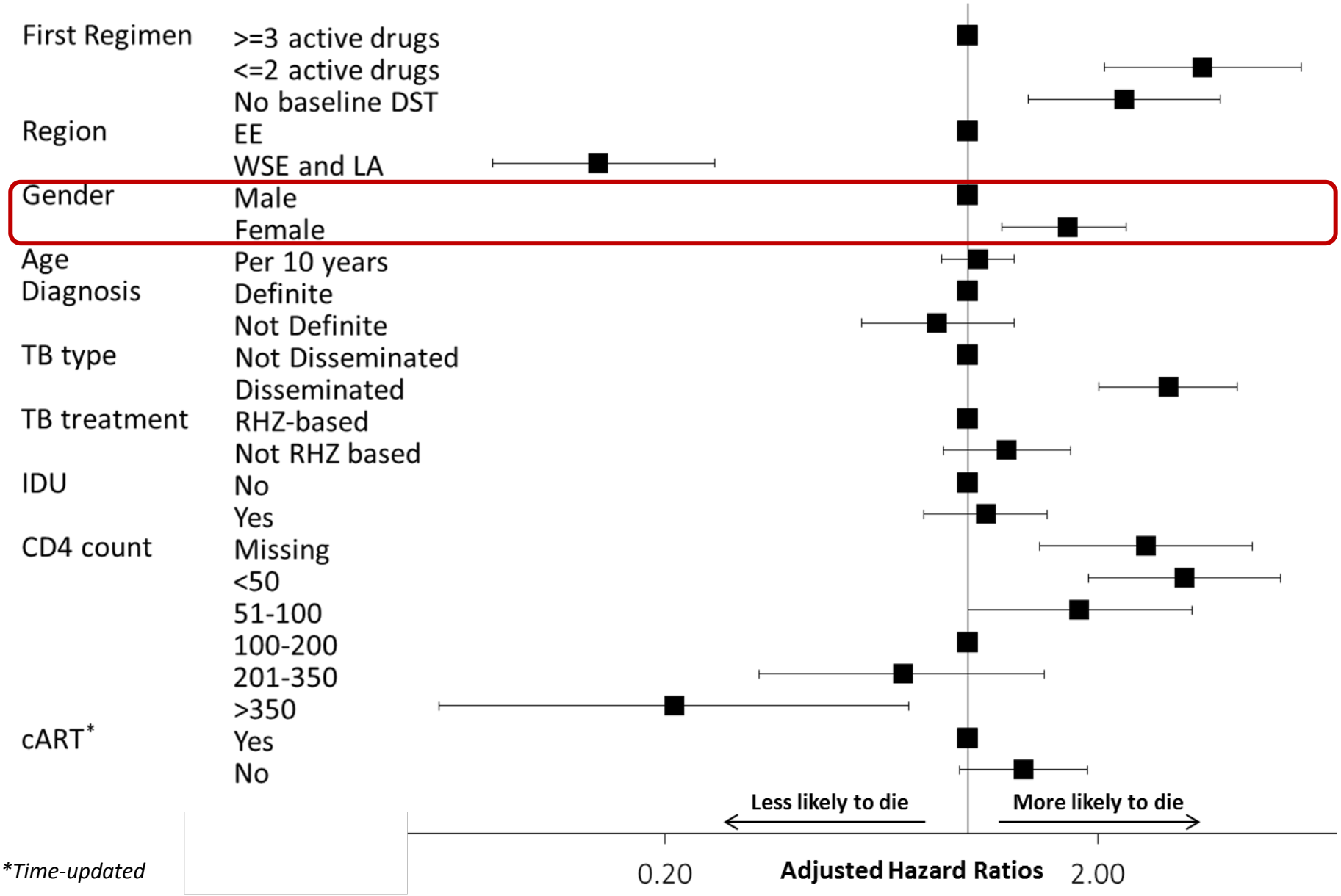

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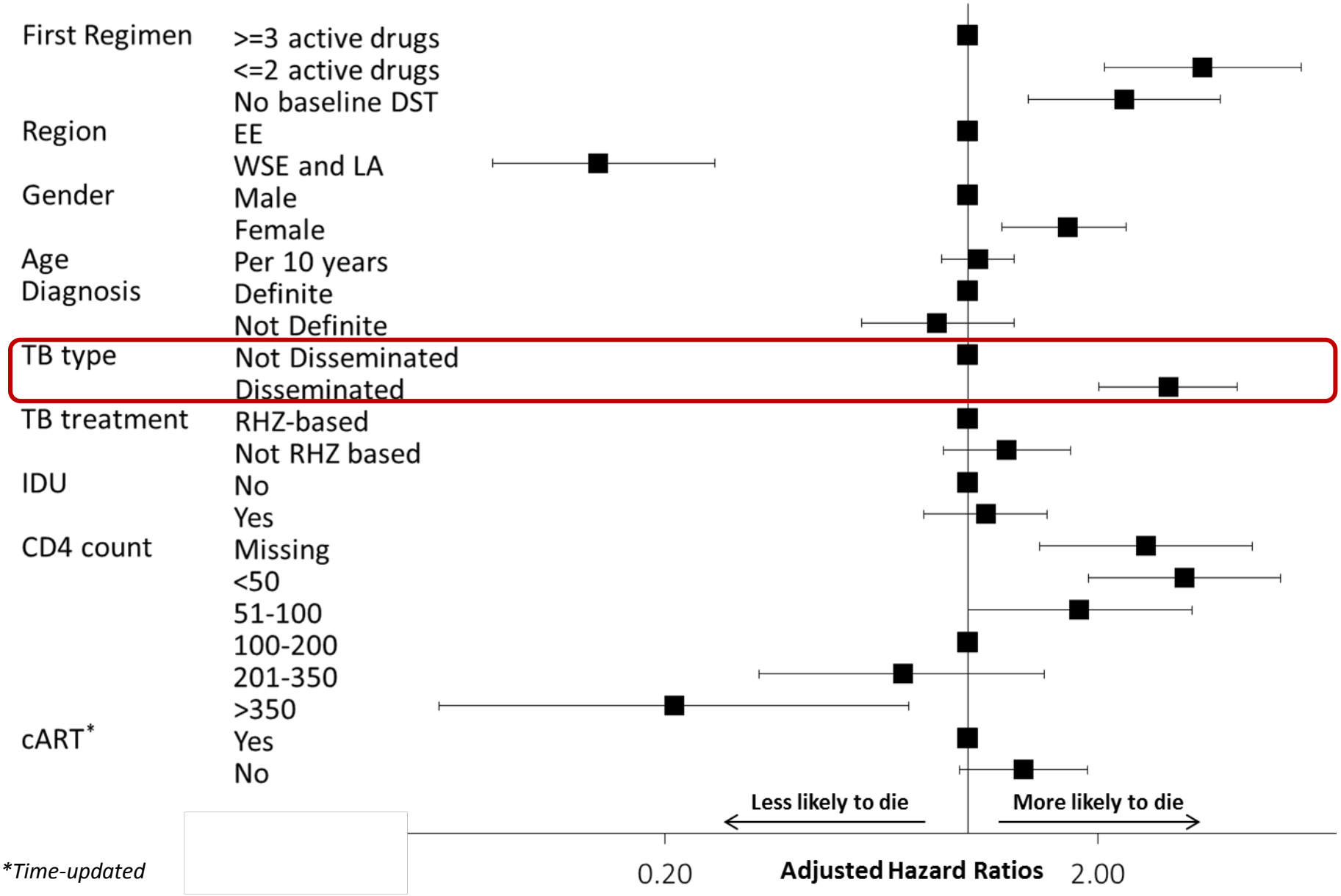

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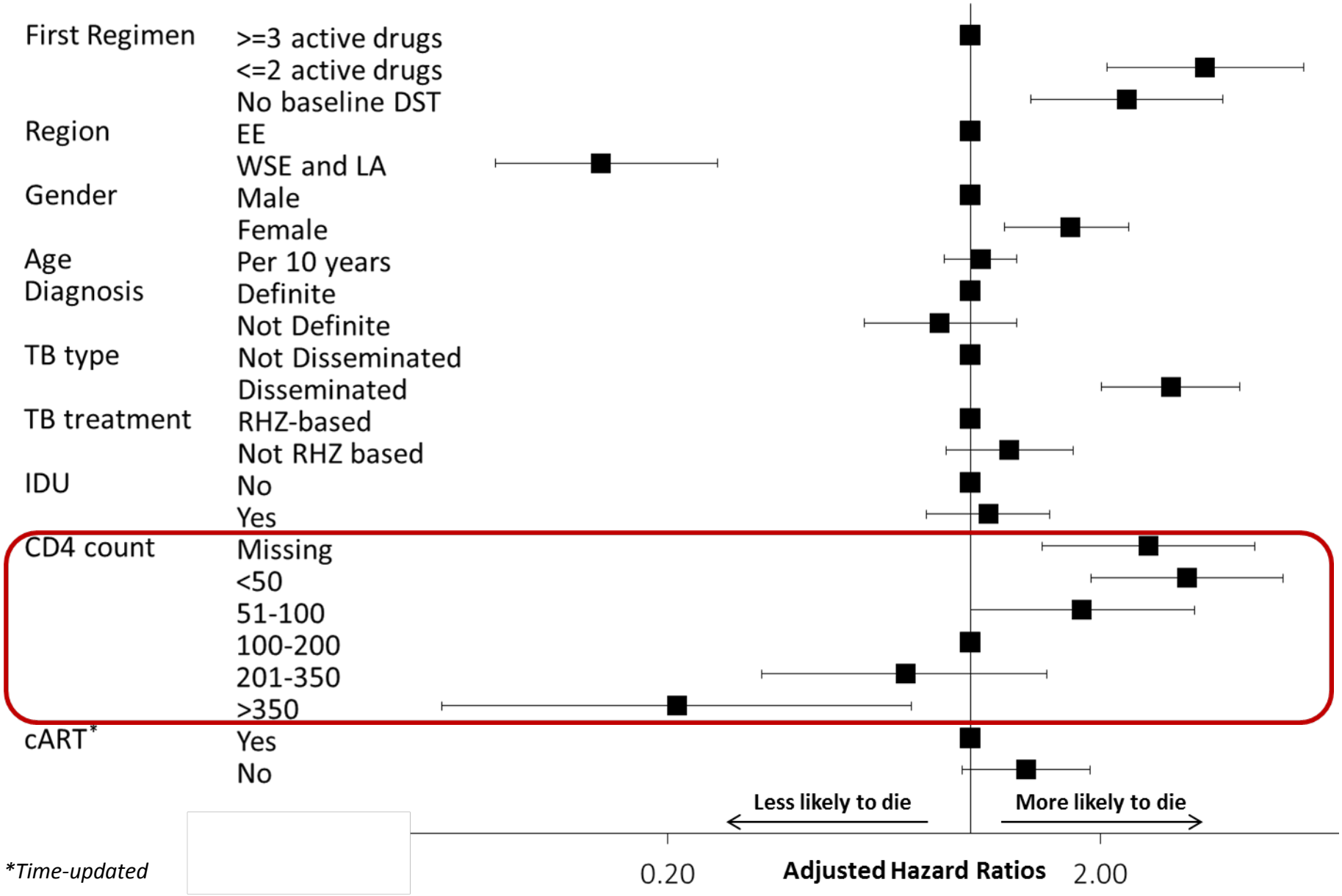

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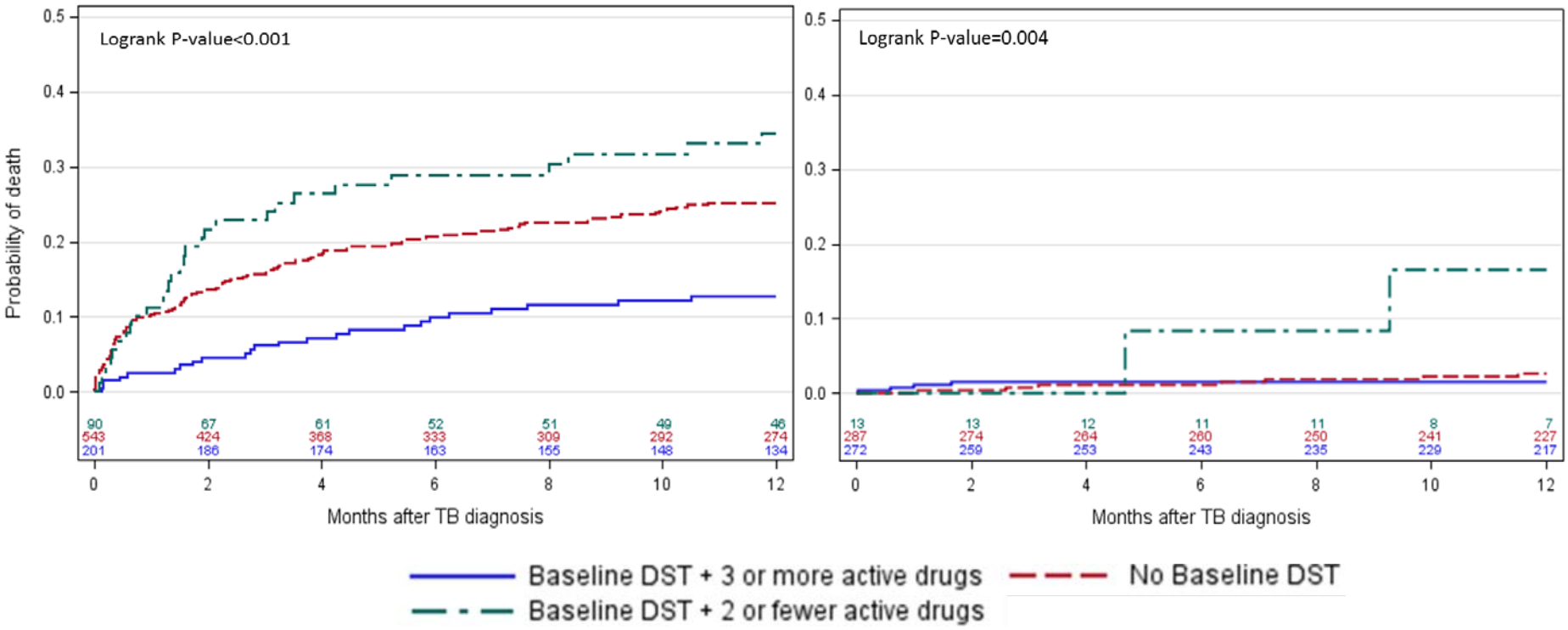
Different effect in different regions?

A) EE:

B) WSE/LA:



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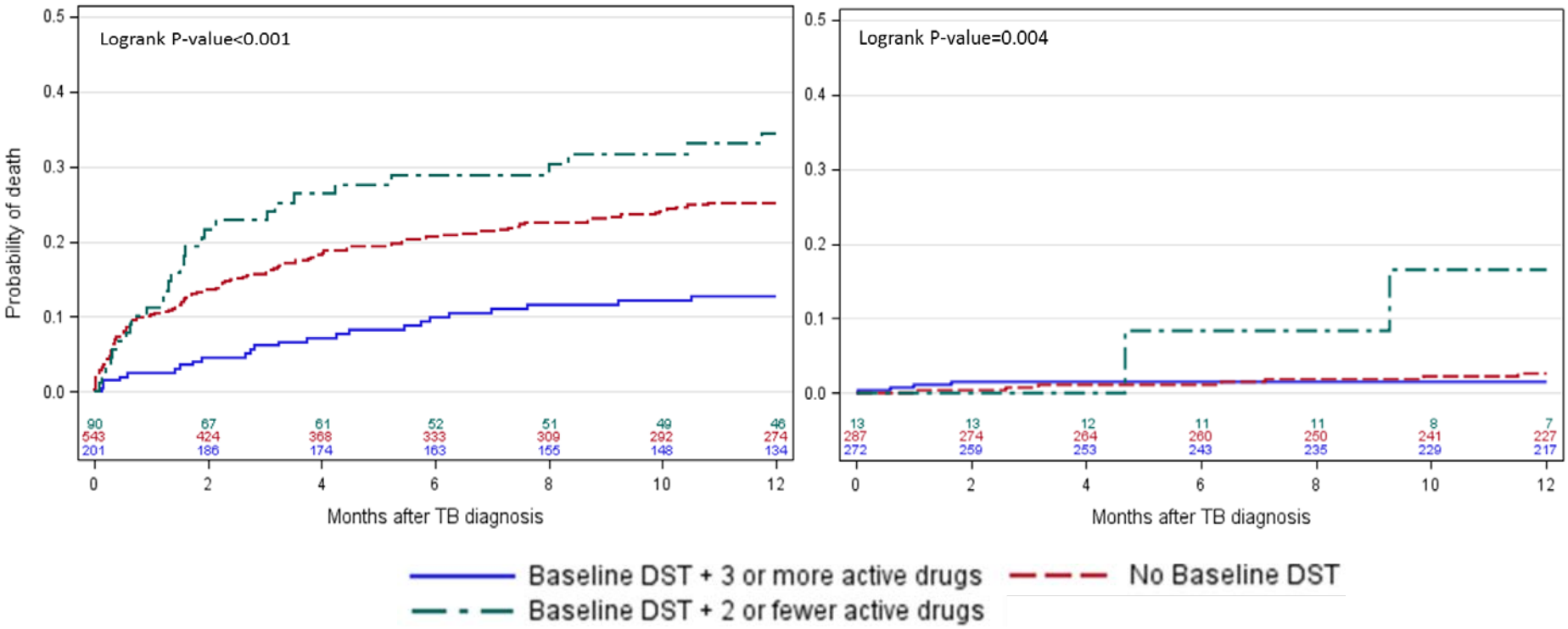

Unadjusted Interaction p-value: **0.20**

Adjusted Interaction p-value: **0.41**

Limitations

- Limited power to study interactions due to few TB deaths occurring outside EE
- Limited ability to study individual countries/clinics
- Generalisability

Summary and Conclusions

- Mortality from TB among people living with HIV in EE countries remains strikingly high
  - 23% at 12 months
- Modifiable risk factors for death identified in this study:
  - Receiving fewer active drugs as a result of MDR-TB
  - Starting an initial regimen composed without DST
  - Low CD4 counts
- Urgent action needed to improve care of TB-HIV co-infected individuals in EE countries
- Integrated response also addressing socioeconomic barriers and challenges within the health systems of each country will be required

TB:HIV an international prospective observational study

The TB:HIV Study Group

Eastern Europe: Belarus: Belarusian State Medical University, Department of Infectious Disease: I Karpov (PI), A Vassilenko; Republican Research and Practical Centre for Pulmonology and TB (Minsk): A Skrahina (PI), D Klimuk, A Skrahin, O Kondratenko and A Zalutskaya; Gomel State Medical University (Gomel): V Bondarenko (PI), V Mitsura, E Kozorez, O Tumash; Gomel Region Centre for Hygiene: O Suetnov (PI) and D Paduto **Estonia:** East Viru Central Hospital (Kohtla-Jarve): V Iljina (PI) and T Kummik **Georgia:** Infectious Diseases, AIDS and Clinical Immunology Research Center (Tiblisi): N Bolokadze (PI), K Mshvidobadze and N Lanchava; National Center for Tuberculosis and Lung Diseases of Georgia (Tibilisi): L Goginashvili, L Mikiashvili and N Bablishvili **Latvia:** Infectology Centre of Latvia (Riga): B Rozentale (PI), I Zeltina and I Janushkevich **Lithuania:** Centre for Communicable Diseases and AIDS (Vilnius): I Caplinskiene (PI), S Caplinskas, Z Kancauskiene **Poland:** Wojewodski Szpital Zakanzy/Medical University of Warsaw (Warszawa): R Podlasin (PI), A Wiercinska-Drapalo (PI), M Thompson and J Kozlowska; Wojewodski Szpital Specjalistyczny/Medical University Teaching Hospital (Bialystok): A Grezeszczuk (PI); Jozef Strus Multidisciplinary City Hospital (Poznan): M Bura (PI); Wroclaw University School of Medicine (Wroclaw): B Knysz (PI) and M Inglot; Jagiellonian University Medical College (Krakow): A Garlicki (PI) and J Loster **Romania:** Dr Victor Babes Hospital (Bucharest): D Duiculescu († PI) and S Tetradov **Russia:** Botkin Hospital of Infectious Diseases (St Petersburg): A Rakhmanova (PI), O Panteleeva, A Yakovlev, A Kozlov, A Tyukalova and Y Vlasova; City TB Hospital No 2 (St Petersburg): A Panteleev (PI); Center for Prevention and Control of AIDS (Veliky, Novgorod): T Trofimov (PI); Medical University Povoljskiy Federal Region **Ukraine:** Crimean Republican AIDS Centre (Simferopol): G Kyselyova (PI)

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