Health Care Delivery for HIV-positive people with tuberculosis in Europe

A Bentzon[1], A Panteleev[2], V Mitsura[3], E Borodulina[4], A Skrahina[5], E Denisova[6], S Tetradov[7], R Podlasin[8], V Riekstina[9], Z Kancauskiene[10], D Paduto[11], A Mocroft[12], T Trofimova[13], R Miller[14], F Post[15], A Grezesczuk[16], JD Lundgren[1], M Inglot[17], D Podlekareva[1], N Bolokadze[18], O Kirk[1] and the TB:HIV Study Group*

*A complete list of members of the study group is listed in an appendix.

Affiliations:

[1]CHIP (Centre of Excellence for Health, Immunity and Infections), Department of Infectious Disease, Rigshospitalet, University of Copenhagen, Denmark. [2]Department of HIV/TB, TB Hospital 2, St Petersburg, Russia.[3]Gomel State Medical University, Gomel, Belarus. [4]Department of Phthisiology and Pulmonology, Samara State Medical University of Minzdrav of Russia, Samara, Russia. [5]Republican Research and Practical Clinic for Pulmonology, Minsk, Belarus. [6]Botkin Hospital of Infectious Disease, St. Petersburg, Russia. [7]Dr. Victor Babes Hospital, Bucharest, Romania. [8]Wojewodski Szpital Zakanzy/Medical University of Warsaw, Warsaw, Poland. [9]Clinic of TB and Lung Diseases, Riga, Latvia. [10]Clinic for Communicable Diseases and AIDS, Vilnius, Lithuania. [11]Gomel Region Clinic for Hygiene, Svetlogorsk, Belarus. [12]Department of Infection and Population Health, University College London, London, United Kingdom. [13]Clinic for Prevention and Control of AIDS, Novgorod, Russia. [14]Mortimer Market Clinic, London, United Kingdom. [15]King's College Hospital, London, United Kingdom. [16]Medical University Teaching Hospital, Bialystok, Poland. [17]Wroclaw University School of Medicine, Wroclaw, Poland. [18]Infectious Diseases, AIDS and Clinical Immunology Research Clinic, Tbilisi, Georgia.

Words:

Manuscript (excl. abstract and references): 3515 words

Abstract: 242 words

Background: In a survey from 2013, we reported distinct discrepancies in the delivery of tuberculosis (TB) and HIV services in Eastern Europe (EE) v. Western Europe (WE)

Objective: To actualize on the differences in TB and HIV services in EE v. WE.

Method: Twenty-three clinics completed a survey in 2018 (EE:14, WE:9, 88% response rate). Results were compared across as well as within the two regions. When possible, results were compared to the survey in 2013.

Results: Delivery of health care was significantly less integrated in EE: provision of TB and HIV services in one clinic (36% in EE v. 89% in WE; p=0.034), and continued TB follow-up in one location (42% v. 100%; p=0.007). Although access to TB diagnostics, standard TB and HIV drugs was generally good, fewer clinics in EE reported unlimited access to rifabutin/MDR-TB drugs, HIV integrase inhibitors and opioid substitution therapy (OST). Compared with 2013, routine usage of GeneXpert was more common in EE in 2018 (54% v. 92%; p=0.073), as was access to moxifloxacin (46% v. 91%, p=0.033), linezolid (31% v. 64%, p=0.217), and bedaquiline (0% v. 25%, p=0.217). Integration of TB and HIV services (46% v. 39%; p=1.000) and provision of OST to patients with opioid dependency (54% v. 46%; p=0.695) remained unchanged.

Conclusion: Delivery of TB and HIV health care including integration of TB and HIV care and access to MDR-TB drugs still differs between WE and EE, as well as between individual EE clinics.

Introduction

In Eastern Europe (EE) the HIV epidemic continues to increase, and a leading cause of death is tuberculosis (TB) (1)(2)(3). Incidences of multi-drug resistant TB (MDR-TB) are high in many countries in EE, with Russia alone accounting for 10% of the world's MDR-TB cases (2). We have previously demonstrated that mortality rates of HIV/TB coinfected patients were considerably higher in EE compared with Western Europe (WE) and this was related to modifiable factors such as lack of drug susceptibility testing (DST) and suboptimal initial TB treatment (3)(4)(5). As a supplement to these results, that were derived from data on individual patients, we investigated provision of HIV and TB services at a clinical level in a survey from 2013. This survey's main findings were; disintegrated health care systems in EE, limited availability of TB drugs for treatment of MDR-TB in EE, low availability of DST for these drugs in EE, and limited availability of opioid substitution therapy (OST) for injecting drug users (IDU) in EE(6). In accordance with these findings, WHO highlights the urgent need of increased access to new TB medicines, higher coverage of DST and a health care system which make it easier to access and continue treatment to improve conditions for people with drug-resistant TB i.e. integrated care (2)(7). Integrated care generally aims at bringing together the delivery of diagnosis, treatment, and rehabilitation, all in order to improve access to health care services and treatment outcome. This cover a broad spectrum from all service being provided by the same care provider to access to all care services within the same health unit.

Since 2013, use of genotypic resistance testing has been widely recommended and TB drugs as moxifloxacin, linezolid, clofazimine, bedaquiline and delamanid have come into broader use(10), and we were therefore interested in knowing whether this has been implemented into clinic-specific guidelines and standard procedures in individual clinics in Europe.
We aimed to compare HIV and TB services provided in clinics in EE and WE and to compare our findings with results from the previous study in 2013.

Methods

The study was a cross-sectional survey and was conducted similarly to the study in 2013 using a slightly modified questionnaire: https://chip.dk/Studies/TBHIV/Documents (6).

Of the 41 European HIV and TB clinics participating in the previously established international 'TB:HIV study collaboration'(11) 26 were invited by email in September 2018 to complete a questionnaire. The 26 clinics included all collaborating EE clinics (except two of five Polish clinics) and 10 WE clinics acting as a reference point. These particular WE clinics were selected to ensure a representative distribution across WE. All participating clinics were larger hospital departments specialized in infectious diseases. Follow-up e-mails and phone calls were used to ensure a high response rate, and data collection within the study was terminated in November 2018.

Data were collected through a self-administered questionnaire consisting of 44 questions divided into 5 categories related to the availability and delivery of HIV and TB health care, as well as to clinical management strategies for coinfected patients (background information, integration of HIV and TB services, utilization of HIV health care, utilization of TB health care and follow-up of TB-HIV coinfected patients).

The responders to the questionnaire were senior consultants in charge of treatment of coinfected patients at the individual clinics. If the HIV and TB services were separated in 2 clinics, only one questionnaire was completed, and responses coordinated in between.

Descriptive categorical data were obtained from the completed questionnaires. All statistical analyses were divided into 2 categories; 1) Comparison between WE and EE clinics 2) Comparison with the 2013 survey.

In order to analyze the overall quality of TB-HIV management within the individual clinics further, a 'TB-HIV care score' was constructed based on 'WHO's rapid communication 2018' recommendations (12). The index includes 4 aspects of care; 1) delivery of health care (max 9 points), 2) TB diagnostics (max 4 points), 3) TB DST availability (max 3 points), and 4) TB drug availability (max 6 points), and a combined score for each clinic was calculated (max 22 points).

The delivery of health care component was based on 13 questions from the questionnaire and covered integration of TB and HIV care, access to OST, payment for care, diagnostic procedures, access to DOT if needed, and procedures in place to avoid loss to follow-up

(question 1, 2, 7, 8, 12, 14, 20, 26, 27, 28, 40, 41 and 43).

The TB diagnostics component was based on 4 questions from the questionnaire and covered standard diagnostic procedures for TB in daily clinical work (question 20, 26, 27, and 28) For further details, please see footnote to figure 2.

The DST component included 3 parts i.e. capability to test for resistance to i) first-line drugs, ii) cycloserine OR terizidone, and iii) at least one injectable AND at least one fluroquinolone.

The drug availability component was composed of 6 bits i.e. unlimited availability to i) first-line drugs, ii) linezolid, iii) clofazimine, iv) bedaquiline, v) cycloserine OR terizidone, and vi) at least one injectable AND at least one fluroquinolone.

Two-sided Fisher's exact test and Independent-Samples T-Test was used to explore associations and calculating p-values. All analyses were performed using SPSS version 24.0.

A power calculation showed that if 99% of the WE clinics had unlimited access to a particular drug, then less than 49% of the EE clinics needed unlimited access in order to demonstrate a significant difference (statistical significance criterion at 0.05).

Results

Of the 26 clinics invited to participate, 23 completed the survey (88% overall response rate), and participating clinics in EE (n=14; 87% response rate) were from Belarus (3), Georgia (1), Latvia (1), Lithuania (1), Poland (3), Romania (1) and the Russian Federation (4). Those in WE (n=9; 90% response rate) were from Belgium (1), Denmark (1), France (1), Italy (1), Spain (2), Switzerland (1), and the United Kingdom (2). Three clinics in Estonia, Crimea, and Italy did not reply.

In total, the EE clinics had an estimated 26.816 HIV-positive patients under regular follow-up with 1229 new TB cases among HIV-positive patients within the last 12 months . Corresponding numbers in WE were 29.548 HIV-positive patients and 94 new TB-HIV patients.

Comparison of delivery of care in Eastern European to Western European clinics

Results on organization and integration of health care services are shown in figure 1. In EE, HIV and TB services were less commonly provided in the same clinic and by the same doctor compared with WE. Most EE clinics reported that TB treatment was initiated at special TB hospitals (79%), whereas in WE, TB treatment was generally initiated in the HIV or infectious diseases clinic (88%; p=0.001). Follow up care for HIV/TB was provided at the same facility in 39% of clinics in EE compared to all clinics in WE (p=0.013). In EE, directly observed therapy (DOT) was more commonly used for the entire duration of TB treatment, in contrast to WE, where DOT was more commonly used for selected patient groups (p=0.006). However, overall usage of any form of DOT did not differ between the two regions.

All clinics reported using guidelines for HIV/TB co-infected patients; national guidelines were more commonly used in EE (100% v. 67%; p=0.047). In addition, use of international (WHO and/or EACS) guidelines was reported by 57% of clinics in EE v. 67% in WE; p=0.495. A similar and high proportion of clinics in the two regions reported that all TB-patients were offered an HIV test (p=1.000). Regular screening of HIV-positive patients for active TB was more commonly performed in EE compared to WE (p=0.081)(figure 1). Use of interferon gamma release assay (IGRA) was less common in EE than in WE (57% v. 100%; p=0.048), where use of tuberculin skin test (TST) was somewhat more common in EE than in WE (57% v. 33%; p=0.400).

Opioid substitution therapy (OST) for all coinfected patients with opioid dependency was only available in some EE clinics, however in all WE clinics (p=0.037). When available, there was no significant difference in how the OST was provided between the two regions. In both regions, most clinics would refer to an OST department (63% v. 67%; p=1.000). There was no significant difference between the two regions regarding standard procedures in place to support adherence or to avoid loss to follow-up (data not shown). However, clinics in WE would, to some degree, more frequently contact other facilities to locate patients lost to follow-up (29% v. 56%; p=0.383).

Comparison of availability of diagnostics and treatments in EE v. WE clinics

Microscopy and culture of sputum were reported to be standard diagnostic procedures for all clinics, and GeneXpert generally accessible in both regions (86% v. 100%; p=0.502). Both regions reported to routinely perform DST at TB diagnosis (86% v. 100%; p=0.502), conventional DST was less commonly used in EE (57% v. 100%; p=0.048), whereas use of GeneXpert seemed more common in EE (86% v. 67%; p=0.343).

There was no significant difference between the two regions' capability to perform DST for individual TB drugs, except for pyrazinamide (54% v. 100%; p=0.046) (table 1). For clofazimine (15% v. 44%), linezolid (23% v. 56%) and bedaquiline (7% v. 22%) substantial non-significant differences between regions were reported.

Two months of isoniazid, ethambutol, pyrazinamide and rifampicin followed by 4 months of rifampicin and isoniazid was generally reported as the standard TB treatment regimen for drug susceptible TB (92% v. 100%; p=1.000), whereas use of a specified standard regimen for MDR-TB was more common in EE (64% v. 13%; p=0.059). Routine evaluation of culture conversion at the end of TB treatment was significantly more common in EE (93% v. 22%; p=0.001).

All EE and WE clinics reported to have unlimited access to isoniazid, ethambutol, pyrazinamide and rifampicin, but availability of rifabutin was low in EE (table 2). Availability of drugs to treat MDR-TB was variable between EE and WE. For drugs such as bedaquiline, linezolid, cycloserine, clofazimine, and carbapenems, there seemed to be profound albeit generally non-significant differences in availability between the two regions (table 2).

Most clinics reported starting antiretroviral therapy (ART) as soon as possible after TB diagnosis, irrespective of CD4 cell count (64% v. 89%; p=0.513). Clinics in EE were more inclined to start a regimen with a non-nucleoside reverse transcriptase inhibitor (almost exclusively efavirenz), whereas integrase strand transfer inhibitors were more popular in WE (p=0.012). Tenofovir disoproxil fumarate + emtricitabine/lamivudine was the most common nucleoside reverse transcriptase inhibitor backbone in both regions (data not shown).

Clinics in EE reported to routinely use of co-trimoxazole for all TB/HIV patients somewhat more often than in WE (46% v. 11%; p=0.165).

The TB-HIV care score for the individual clinics ranged from 10 to 21 with a mean in WE of 19.1±0.7 (standard error) points and 15.0±0.7 in Eastern Europe, (p=0.001) (figure 2).
In WE, 8 of 9 (88.9%) had a TB-HIV care score of ≥17 compared with 3 of 13 (23.1%) with some variation in the segments of the score for the individual clinic. For delivery of health care/integration of care, all clinics in WE had at least 8 points. Only 2 EE clinics had 8 points, the remaining 11 clinics had between 3 and 6 points.
One EE clinic had a score of 6 due to 9 missing values and was excluded from the analysis. Within EE, the score varied from 10 to 19 with considerable heterogeneity within the region; 3 had a score ≥17, 6 had a score of 14-16, and the remaining 4 had a score of 10-13.

Comparison of data from the 2013 and 2018 surveys

Twenty-one clinics participated in both surveys and were included in these analyses; 13 clinics from EE (Georgia, Latvia, Lithuania, Romania (all n=1), and Belarus, Poland and the Russian Federation (3 each), and 8 clinics from WE (Belgium, Denmark, France, Italy, Spain, Switzerland (all 1) and the United Kingdom (2).
In EE, there was no improvement in integration of TB and HIV services, and patients were even less likely to be treated for TB and HIV by the same doctor (figure 3). Use of OST did not increase between 2013 and 2018. When looking at the component of delivery/integration of care of the TB-HIV care score, only 3 EE clinics had an increase in this sub-score from 2013 to 2018 (data not shown).
Access to GeneXpert improved substantially from 2013 to 2018 (54% v. 92%; p=0.073). The standard TB treatment remained unchanged, although there was a tendency to add second

line TB drugs to the initial regimen (0% v. 18%; p=0.082). A culture conversion test was used at the end of treatment in all but one clinic in 2018, compared with 9 of 13 in in 2013 (p=0.322). Development in access to TB drugs is illustrated in figure 4. Unlimited access to TB drugs improved significantly for moxifloxacin, but also seemed to improve for rifabutin, levofloxacin, ethionamide, prothionamide, linezolid and bedaquiline, although not significantly so figure 4.

The only notable change in WE clinics was an improved access to bedaquiline (0% v. 50%; p=0.050).

As for HIV treatment strategies, there was a trend towards earlier initiation of ART in 2018, defined as 'as soon as possible and within the first 8 weeks after TB diagnosis, regardless of CD4 cell count' (46% v. 62%; p=0.134).

Discussion

This clinical survey suggests that while considerable progress in areas such as HIV testing of TB patients and access to first line TB treatment has been made in EE, HIV and TB care remains fragmented and access to MDR-TB treatment highly variable. Delivery of health care was considerably more fragmented in EE than WE, with TB treatment, follow-up, ART, and OST being provided at different sites and by different health care professionals. When combining survey variables in a TB-HIV care score, WE clinics in general had a higher score than EE clinics, and the score varied substantially in EE. Some clinics in EE were close to having the same TB-HIV care score as WE clinics, whereas other clinics were lacking considerably behind. It was not possible to identify a threshold for good clinical practice, but it is worth noting that 8/9 clinics in WE had a score of 17 or more, which may suggest this is an acceptable level for a clinic. Our results supplement a survey from 2016/2017 by the Wolfheze Working Group (13) that focuses on the programmatic aspects, i.e. policies and guidelines on management of coinfected patients, whereas our study focuses on data on the actual daily practical management, i.e. on the organizational aspects. Both studies found that all countries have guidelines for management of coinfected patients, whereas our survey also documents that usage of such national guidelines was more common in EE compared with WE. And both report on fragmented health care delivery in EE. In recent

decades, numerous definitions of 'integrated care' have been put forward (8) however a detailed discussion of these is beyond the scope of this study. In short, some of the general approaches to 'integrated care' are; 1) merging of departments; 2) establishing guidelines on specific health issues; 3) and collaboration across services, e.g. between health care professionals and social workers(8)(14). A review of 17 systemic reviews on integrated care concluded that health care integration potentially improves delivery of health care and treatment outcome (9). Whereas the benefits of integrated services are well described, potential TB transmission among HIV-positive people in integrated TB/HIV clinics is a concern, and relevant measures such as use of masks, good hygiene and isolation should be taken to reduce this risk. Still, the most recent WHO guidelines on management of TB/HIV patients highlight delivering integrated services as an important tool to reduce the burden of disease(15). This recommendation is supported by a study from 2007, in which co-location of TB/HIV services was associated with improved medical adherence and clinical outcomes(16). The lack of improvement in TB-HIV health care delivery in most EE clinics contrasts these recommendations and calls for action now, requiring profound changes in health care infrastructure.

It has been suggested that DOT, which is significantly more commonly used in EE than WE, to some degree can compensate for a fragmented health care system regarding medical adherence. A review from 2015 found that DOT improved adherence compared to self-administered treatment, but this effect was lost as contact to health care facilities became more frequent, and considering the cost implications, DOT did not provide a solution to poor adherence to TB treatment (17).

Our results document that access to OST in EE, which is an important component of care for HIV-positive people who inject drugs, has not improved from 2013 to 2018. The continuous restricted use of OST in EE is problematic for the health of individual patients and for the continuous HIV transmission among IDUs in EE (18).

Numerous studies have shown that OST decreases the spread of HIV and increases adherence to ART(19)(20)(21)(22). OST is still formally illegal in the Russian Federation(23), but even in other countries, usage remains limited signifying that is not only an issue of legality. A recent systematic review acknowledges integration of health care, client centered philosophies, and attention to stigma as aspects that affect usage of OST (24).

The general TB diagnostic and treatment approach did not differ between clinics in EE and WE, and our results suggest that GeneXpert has become widely available across EE. Although this reflects excellent progress, the high prevalence of MDR-TB (and likely high levels of XDR-TB) in EE calls for rapid genotypic DST beyond rifamycins (e.g. line-probe assay for FQs and SLIs), and additional measures such as coordination of MDR-TB care through virtual review in clinics of excellence, which may allow rapid test information to be optimally used to design MDR-TB regimens and provide access to such regimens. The observed common practice in EE of adding one or more second-line drugs to the initial treatment, perhaps based on GeneXpert results or clinical suspicion of resistant TB, is of potential concern but cannot be further analyzed in the present study.

There were no significant regional differences in access to DST for most TB drugs, although fewer clinics in EE had access to DST for rifabutin, linezolid, clofazimine, bedaquiline, but not significantly so, perhaps due to the limited number of clinics included.

A similar pattern was observed for unlimited access to individual TB drugs, with lower levels of unlimited availability of rifabutin and clofazimine in EE, contrasting findings for the 2013 survey where EE clinics had significantly less access to most drugs with activity against MDR-TB (6). Unlimited access to DST and TB drugs including in particular the new WHO-recommended key components of MDR-TB treatment regimens such as levofloxacin/moxifloxacin, bedaquiline, linezolid, clofazimine, cycloserine/terizidone (25) seems crucial if patient care and treatment outcome in EE are to be improved.

Compared to the 2013 survey, EE clinics were more inclined to initiate ART as soon as possible, reflecting that results from large randomized trials have changed clinical practice (26)(27)(28). In EE, efavirenz is still the preferred third component in half of the EE clinics, although dolutegravir and raltegravir seem like attractive first choices due to a more favorable toxicity profile, especially for TB/HIV coinfected people, and IDUs, and due to few drug-drug-interactions.

There are some limitations to this study. It is based on self-reported data and therefore sensitive to information biases including ‘obsequiousness bias’, where people systematically adjust their responses to fit the expected desire of the investigator. To address this, we visited 8 EE clinics and interviewed staff that completed the survey. In general, there were only few and minor discrepancies, which seemed to be due to differences in interpretation

of a few questions in the survey. It is therefore likely that the survey data generally represents the local practices in the participating clinics, although slight overestimation of the surveyed clinics' capability cannot be excluded.

Another limitation is that the collaborating EE clinics in general are major clinics or referral hospitals and therefore not necessarily representative of the entire EE health care system for TB-HIV patients, but rather reflect best standard in their respective countries. It is worth noting that the response rate to the survey was high, and results are likely to reflect the situation at all clinics in the TB:HIV Study.

Finally, since the survey was completed by 23 clinics, the statistical power is limited, as illustrated by relatively large, but insignificant, differences in for example access to individual TB drugs. The statistical analyses were not corrected for multiple testing, and there is a risk of type 1 error, so that the significant results should interpreted conservatively.

To conclude, this clinic-based survey has demonstrated persistent and significant differences in health care management for TB-HIV-patients across Europe, but also significant improvements in Eastern Europe. GeneXpert and TB drugs with activity against MDR-TB are now more commonly used in EE which if combined with future improvements in integration of TB and HIV services and patient support - may potentially lead to improved diagnostics, health care, personalized treatment, and ultimately treatment outcome for future TB-HIV-patients in Eastern Europe. However, the survey also showed considerable heterogeneity within EE, and in some EE clinics care is still far from the level in WE.

Drug	Eastern Europe (n=14, % of clinics)	Western Europe (n=9, % of clinics)	p-value
Isoniazid	92.3	100	1.000
Ethambutol	84.6	100	0.494
Pyrazinamide	53.8	100	0.046
Rifampicin	92.3	100	1.000
Rifabutin	30.8	44.4	0.662
Streptomycin	57.1	66.7	0.495
Injectables (any)	100	100	NA
Fluoroquinolone (any)	84.6	100	0.494
Ethionamide or Prothionamide	76.9	77.8	1.000
Cycloserine	61.5	55.6	1.000
Terizidone	14.3	22.2	1.000
Clofazimine	15.4	44.4	0.178
P-aminosalicyclic acid	64.3	33.3	0.214
Linezolid	23.1	55.6	0.187
Bedaquiline	7.1	22.2	0.538
Delamanid	7.1	0	1.000

Table 1. Availability of TB drug susceptibility testing in daily clinical work in clinics in EE and WE. Any injectable; amikacin, kanamycin or capreomycin. Any fluoroquinolone; ciprofloxacin, levofloxacin, moxifloxacin or ofloxacin.

Drug	Eastern Europe (n=14, % of clinics)	Western Europe (n=9, % of clinics)	p-value
Rifampicin, Isoniazid, Pyrazinamide and Ethambutol	100	100	NA
Rifabutin	23.1	88.9	0.008
Streptomycin	61.5	83.3	0.605
Amikacin	100	88.9	0.409
Kanamycin	69.2	50.0	1.000
Viomycin	0	20.0	0.294
Capreomycin	58.3	50.0	1.000
Ciprofloxacin	75.0	85.7	1.000
Levofloxacin	92.3	75.0	0.531
Moxifloxacin	91.7	88.9	1.000
Ofloxacin	75.0	66.7	1.000
Cycloserine	66.7	87.5	0.603
Terizidone	25.0	20.0	1.000
Clofazimine	27.3	87.5	0.020
Ethionamide	50.0	57.1	1.000
Prothionamide	83.3	57.1	0.305
Linezolid	58.3	88.9	0.178
P-aminosalicylic acid	66.7	71.4	1.000
Amoxicillin	84.6	87.5	1.000
Meropenem	33.3	77.8	0.080
Imipenem	53.8	85.7	0.329
Delamanid	16.7	22.2	1.000
Bedaquiline	23.1	44.4	0.376

Table 2. TB drug availability in clinics in EE and WE. *p<0.05.

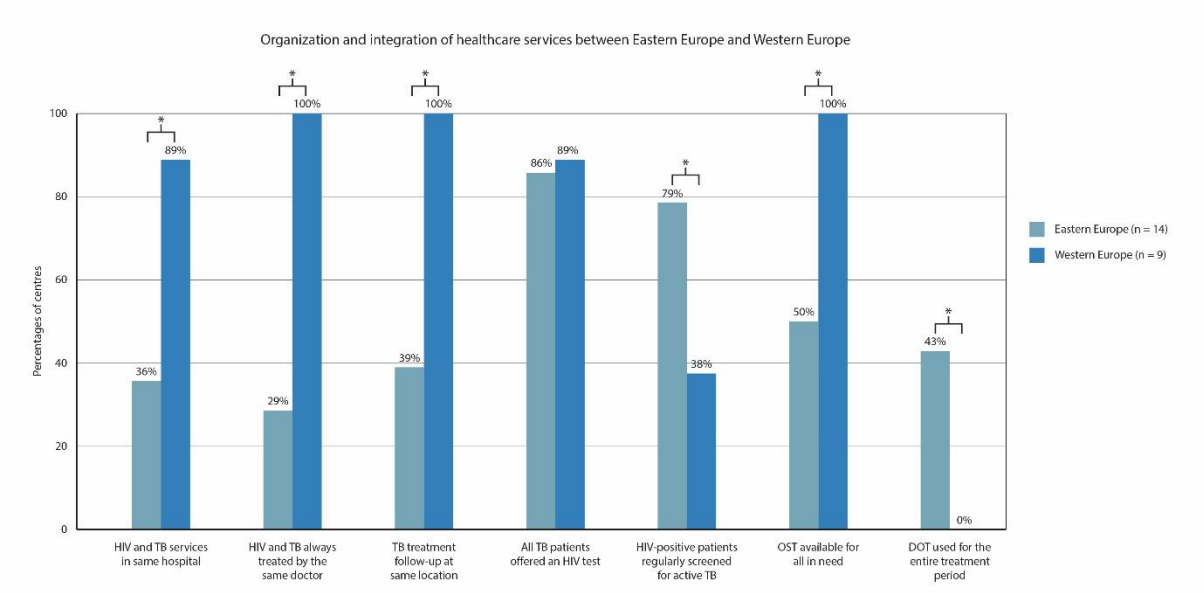

Figure 1. Organization and integration of health care services between EE and WE.

*p<0.05.

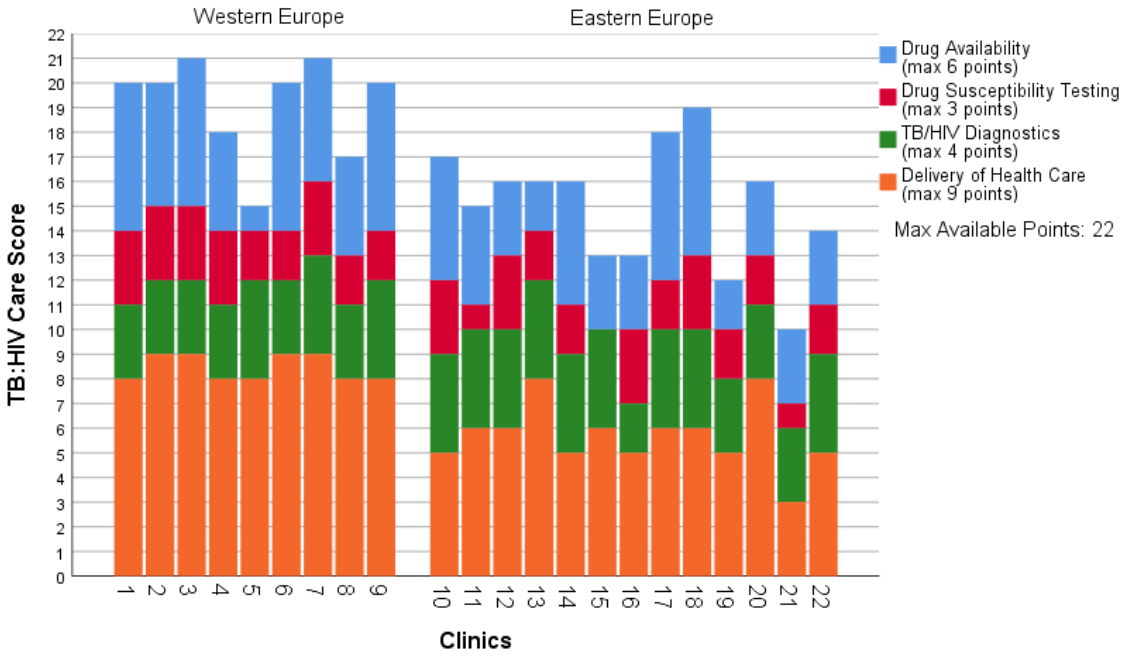

Figure 2. Health Care Index. Delivery of health care; composed of 13 components from the questionnaire (Question 1, 2, 7, 8, 12, 14, 20, 26, 27, 28, 40, 41 and 43). 1 point granted if the following criteria were met:

Question 1: HIV and TB services located within one hospital.

Question 2: HIV and TB usually treated by the same doctor.

Question 7: OST available for all in need.

Question 8: All patients diagnosed with TB offered HIV testing.

Question 12: No fee for HIV services

Question 14: Initiation of ART treatment as soon as possible after TB diagnosis.

Question 40: Usage of any form of DOT.

Question 41: Patient follow-up at the same hospital for the entire period of TB treatment.

Question 43: Procedures in place to prevent loss to follow-up.

TB diagnostics; composed of 4 questions from the questionnaire (question20, 26, 27 and 28). 1 point granted if the following criteria were met:

Question 20: HIV patients regularly screened for active TB disease.

Question 26: NAAT, culture, microscopy followed by NAAT/culture or NAAT followed by culture is standard diagnostic procedure for TB.

Question 27: Access to rapid TB diagnostic test.

Question 28: DST routinely performed for all positive cultures.

DST; composed of 3 components i.e. capability to test for resistance to i) first-line drugs, ii) cycloserine OR terizidone, and iii) at least one injectable AND at least one fluroquinolone.

Drug availability; composed of 6 components i.e. unlimited availability to i) first-line drugs, ii) linezolid, iii) clofazimine, iv) bedaquiline, v) cycloserine OR terizidone, vi) and at least one injectable AND at least one fluroquinolone.

Missing values; Clinic no. 2, 8 and 10 had 1 missing value, and clinic no. 19 had 3 missing values.

One EE clinic excluded from this analysis due to 9 missing values.

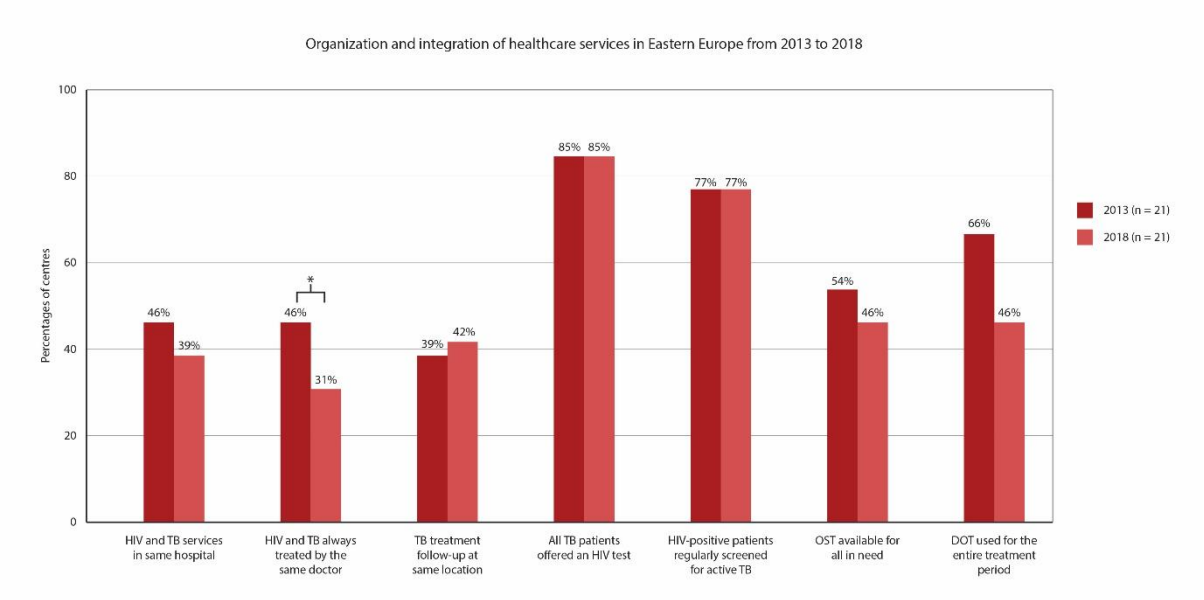

Figure 3. Comparison of **Organization and integration of health care services in EE in 2013 v. 2018.** *p=0.05.

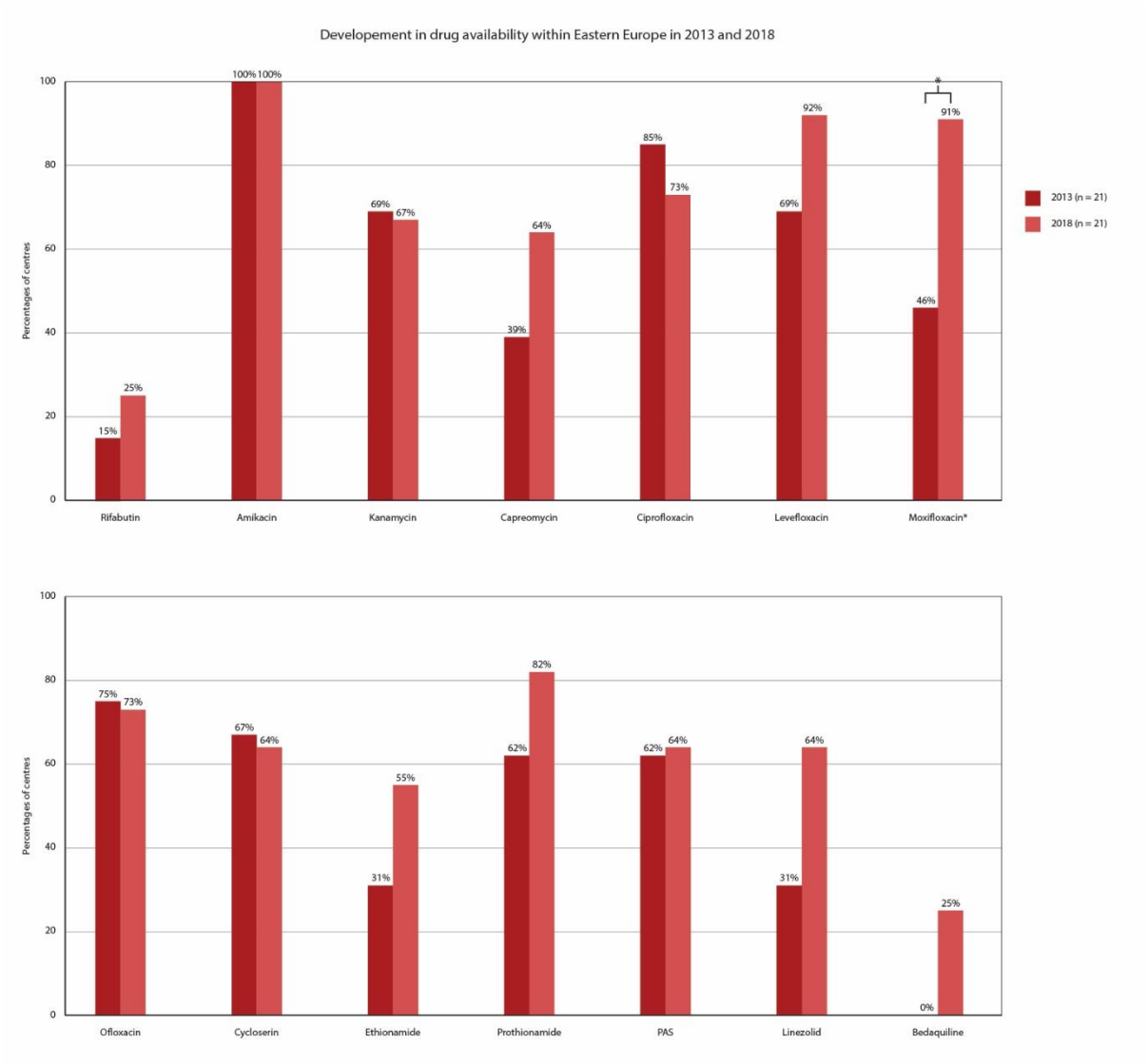

Figure 4. Developments in drug availability within EE from 2013 to 2018. *p<0.05. PAS, P-aminosalicylic acid. Data on individual drugs was only included if collected in both surveys.

References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Data 2017. Program HIV/AIDS [Internet]. 2017;1–248. Available from: http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf
2. WHO Global tuberculosis report 2018.
3. Podlekareva DN, Mocroft A, Post FA, Riekstina V, Miro JM, Furrer H, et al. Mortality from HIV and TB coinfections is higher in Eastern Europe than in Western Europe and Argentina. AIDS. 2009 Nov;23(18):2485–95.
4. Podlekareva DN, Panteleev AM, Grint D, Post FA, Miro JM, Bruyand M, et al. Short- and long-term mortality and causes of death in HIV/tuberculosis patients in Europe. Eur Respir J. 2014 Jan;43(1):166–77.
5. Podlekareva DN, Efsen AMW, Schultze A, Post FA, Skrahina AM, Panteleev A, et al. Tuberculosis-related mortality in people living with HIV in Europe and Latin America: an international cohort study. lancet HIV. 2016 Mar;3(3):e120-31.
6. Mansfeld M, Skrahina A, Shepherd L, Schultze A, Panteleev AM, Miller RF, et al. Major differences in organization and availability of health care and medicines for HIV/TB coinfected patients across Europe. HIV Med. 2015 Oct;16(9):544–52.
7. Geneva: World Health Organization. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis: 2011 Update. Geneva; 2011.
8. WHO/Europe | Health services delivery - Integrated care models: an overview (2016) [Internet]. [cited 2020 Jul 23]. Available from: https://www.euro.who.int/en/health-topics/Health-systems/health-services-delivery/publications/2016/integrated-care-models-an-overview-2016
9. Heyeres M, McCalman J, Tsey K, Kinchin I. The complexity of health service integration: A review of reviews [Internet]. Vol. 4, Frontiers in Public Health. Frontiers Media S. A; 2016 [cited 2020 Jul 23]. p. 223. Available from: /pmc/articles/PMC5066319/?report=abstract

10. WHO treatment guidelines for drug- resistant tuberculosis 2016. Geneva; 2016.

11. CHIP – Centre of Excellence for Health, Immunity and Infections [Internet]. [cited 2019 Jan 2]. Available from: https://chip.dk/Studies/TBHIV/TBHIV-Study-Group

12. WHO | Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). WHO [Internet]. 2018 [cited 2019 Sep 22]; Available from: https://www.who.int/tb/publications/2018/rapid_communications_MDR/en/

13. A Survey on Collaborative TB/HIV Activities in Countries of the WHO European Region - AFEW International [Internet]. [cited 2019 Oct 14]. Available from: http://afew.org/headlines/tb-hiv-activities-eng/

14. World Health Organization. Integrated health services – what and why ? Tech Br. 2008;(1):1–8.

15. Geneva: World Health Organization. WHO Policy on Collaborative TB/HIV Activities: Guidelines for National Programmes and Other Stakeholders. Geneva; 2012.

16. Sylla L, Bruce RD, Kamarulzaman A, Altice FL. Integration and co-location of HIV/AIDS, tuberculosis and drug treatment services. Int J Drug Policy. 2007 Aug;18(4):306–12.

17. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane database Syst Rev. 2015 May;(5):CD003343.

18. HIV/AIDS surveillance in Europe 2018 - 2017 data [Internet]. [cited 2019 Sep 23]. Available from: https://ecdc.europa.eu/en/publications-data/hivaids-surveillance-europe-2018-2017-data

19. Spire B, Lucas GM, Carrieri MP. Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST). Int J Drug Policy. 2007 Aug;18(4):262–70.

20. Strathdee SA, Hallett TB, Bobrova N, Rhodes T, Booth R, Abdool R, et al. HIV and risk environment for injecting drug users: the past, present, and future. Lancet (London, England). 2010 Jul;376(9737):268–84.

21. Roux P, Carrieri MP, Cohen J, Ravaux I, Poizot-Martin I, Dellamonica P, et al. Retention in opioid substitution treatment: a major predictor of long-term virological success for HIV-infected injection drug users receiving antiretroviral treatment. Clin Infect Dis.

2009 Nov;49(9):1433–40.

22. Bachireddy C, Soule MC, Izenberg JM, Dvoryak S, Dumchev K, Altice FL. Integration of health services improves multiple healthcare outcomes among HIV-infected people who inject drugs in Ukraine. Drug Alcohol Depend. 2014 Jan;134:106–14.

23. Idrisov B, Murphy SM, Morrill T, Saadoun M, Lunze K, Shepard D. Implementation of methadone therapy for opioid use disorder in Russia - a modeled cost-effectiveness analysis. Subst Abuse Treat Prev Policy. 2017 Jan;12(1):4.

24. Guise A, Seguin M, Mburu G, McLean S, Grenfell P, Islam Z, et al. Integrated opioid substitution therapy and HIV care: a qualitative systematic review and synthesis of client and provider experiences. AIDS Care. 2017 Sep;29(9):1119–28.

25. WHO | WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update. WHO [Internet]. 2018 [cited 2019 Jan 26]; Available from: https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/gdg-meeting-mdr-rr-tb-treatment-2018-update/en/

26. Blanc F-X, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med. 2011 Oct;365(16):1471–81.

27. Havlir D V, Kendall MA, Ive P, Kumwenda J, Swindells S, Qasba SS, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med. 2011 Oct;365(16):1482–91.

28. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med. 2011 Oct;365(16):1492–501.

Appendix

TB:HIV study group:

Eastern Europe

Belarus: Belarusian State Medical University, Department of Infectious Disease: I. Karpov (PI), A. Vassilenko (site coordinator); Republican Research and Practical Clinic for Pulmonology (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 Clinic 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 Clinic (Tiblisi): N. Bolokadze (PI), K. Mshvidobadze and N. Lanchava; National Clinic for Tuberculosis and Lung Diseases of Georgia (Tibilisi): L. Goginashvili, L. Mikiashvili and N. Bablishvili.

Latvia: Infectology Clinic of Latvia (Riga): B. Rozentale (PI), I. Zeltina and I. Janushkevich.

Lithuania: Clinic 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. Grezesczuk (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; Clinic for Prevention and Control of AIDS (Veliky, Novgorod): T. Trofimov (PI); Medical University Povoljskiy Federal Region.

Ukraine: Crimean Republican AIDS Clinic (Simferopol): G. Kyselyova (PI).

Central Northern Europe

Denmark: Rigshospitalet (Cph): N. Obel (PI) and J. Gerstoft; Hvidovre University Hospital: G. Kronborg.

Belgium: CHU Saint-Pierre (Brussels): MC Payen (PI), K. Kabeya and C. Necsoi.

France: Aquitaine Cohort: Cohorte administration: F. Dabis (PI) and A. Tsaranazy (public health resident). Participating Clinics and Physicians: Bayonne Hospital; Bordeaux University Hospital: C. Cazanave.

Switzerland: Swiss HIV Cohort Study (SHCS): Cohorte administration: H. Furrer (PI), M. Sagette (site manager) and M. Rickenbach (head data clinic). Participating Clinics and Physicians: University Hospital Basel: L. Elzi and M. Battegay; University Hospital Bern: H. Furrer; Hopital Cantonal Universitaire, Geneve: D. Sculier and A. Calmy; Clinic Hospitalaire Universitaire Vaudois, Lausanne: M. Cavassini; Hospital of Lugano: A. Bruno and E. Bernasconi; Cantonal Hospital St. Gallen: M. Hoffmann and P. Vernazza; University Hospital Zurich: J. Fehr and Prof. R. Weber.

United Kingdom: Mortimer Market Clinic (London): R. Miller (PI) and N. Vora; St. Mary's Hospital: G. Cooke (PI) and S. Mullaney; North Manchester General Hospital: E. Wilkins (PI) and V. George; Sheffield Teaching Hospitals: P. Collini (PI) and D. Dockrell; King's College Hospital (London): F. Post (PI), L. Campbell, R. Brum, E. Mabonga and P. Saigal. Queen Elizabeth Hospital: S. Kegg (PI); North Middelsex University Hospital: J. Ainsworth (PI) and A. Waters. Leicester Royal Infirmary: J. Dhar (PI) and K. Ellis.

Southern Europe

Italy: IRCCS - Ospedale L. Spallanzani (Rome): E. Girardi (PI), A Rianda, V. Galati, C. Pinnetti and C. Tommasi; AO San Gerardo (Monza): G. Lapadula (PI); IRCCS AOU San Martino – IST di Genoa (Genova): A. Di Biagio (PI) and A. Parisini; Clinic of Infectious Diseases, University of Bari (Bari): S. Carbonara (PI), G. Angarano and M. Purgatorio; University of Brescia Spedali Civili: A. Matteelli (PI) and A. Apostoli.

Spain: Barcelona Cohort funded by the Spanish HIV/AIDS Research Network: Hospital Clinic of Barcelona: JM. Miro (PI), C. Manzardo, C. Ligero and J. Gonzalez and Jose A. Martinez-Martinez; Hospital del Mar: F. Sanchez, H. Knobel, M. Salvadó and J.L. Lopez-Colomes; Mutua de Terrassa: X. Martínez-Lacasa and E. Cuchí; Hospital Universitari Vall d'Hebrón: V. Falcó, A. Curran, M.T. Tortola, I. Ocaña and R. Vidal; Hospital Universitari de la Santa Creu i Sant Pau: MA. Sambeat, V. Pomar and P. Coll; Hospital Universitari de Bellvitge: D. Pozamczer, M. Saumoy and F. Alcaide; Agencia de Salud Pública de Barcelona: J. Caylà, A. Moreno, J.P. Millet, A. Orcau, L. Fina, A. Romero, L.L. Roldan. Hospital Universitaria Donostia (San Sebastian): JA. Iribarren (PI) and M. Ibarguren; Hospital Ramon y Cajal (Madrid): S.

Moreno (PI) and A. González; Hospital Universitaria 'Gregorio Marañon'' (Madrid): P. Miralles (PI) and T. Aldámiz-Echevarría.

Latin America:

Argentina: The CICAL Cohort: Cohorte administration: M. Losso (PI), J. Toibaro and L. Gambardella. Participating Clinics and Physicians: Hospital J. M. Ramos Mejía (Buenos Aires): J. Toibaro and L. Moreno Macias; Hospital Paroissien (BA): E. Warley (PI) and S. Tavella; Hospital Piñero (BA): O. Garcia Messina and O. Gear; Hospital Nacional Profesor Alejandro Posadas: H. Laplume; Hospital Rawson (Cordoba): C. Marson (PI); Hospital San Juan de Dios (La Plata): J. Contarelia and M. Michaan; Hospital General de Agudos Donación F. Santojani: P. Scapellato; Hospital Francisco Javier Muñiz (BA): B. Bartoletti and D. Palmero; Hospital Jujuy: C. Elias.

Chile: Fundación Arriaran (Santiago): C. Cortes.

México: INNcMZS (México DF): B. Crabtree (PI); Hospital General Regional de Leon-CAPACITS: JL Mosqueda Gomez; Hospital Civil de Guadalajara: J. A. Villanueva (PI); LA Gonzalez Hernandez and F. Badial