ORIGINAL RESEARCH

Improving healthcare for patients with HIV, tuberculosis and hepatitis C in eastern Europe: a review of current challenges and important next steps

Christian Kraef1,2,3 | Adrian Bentzon1 | Alena Skrahina4 | Amanda Mocroft1,5 | Lars Peters1 | Jens D. Lundgren1,2 | Nikoloz Chkhartishvili6,7 | Daria Podlekareva1,2 | Ole Kirk1,2

Abstract

Objectives: In some eastern European countries, serious challenges exist to meet the HIV-, tuberculosis (TB)- and hepatitis-related target of the United Nations Sustainable Development Goals. Some of the highest incidence rates for HIV and the highest proportion of multi-drug-resistant (MDR) tuberculosis worldwide are found in the region. The purpose of this article is to review the challenges and important next steps to improve healthcare for people living with TB, HIV and hepatitis C (HCV) in eastern Europe.

Methods: References for this narrative review were identified through systematic searches of PubMed using pre-identified key word for articles published in English from January 2000 to August 2020. After screening of titles and abstracts 37 articles were identified as relevant for this review. Thirty-eight further articles and sources were identified through searches in the authors’ personal files and in Google Scholar.

Results: Up to 50% of HIV/MDR-TB-coinfected individuals in the region die within 2 years of treatment initiation. Antiretroviral therapy (ART) coverage for people living with HIV (PLHIV) and the proportion virological suppressed are far below the UNAIDS 90% targets. In theory, access to various diagnostic tests and treatment of drug-resistant TB exists, but real-life data point towards inadequate testing and treatment. New treatments could provide elimination of viral HCV in high-risk populations but few countries have national programmes.

Conclusion: Some eastern European countries face serious challenges to achieve the sustainable development goal-related target of 3.3 by 2030, among others, to end the epidemics of AIDS and tuberculosis. Better integration of healthcare systems, standardization of health care, unrestricted substitution therapy for all people who inject drugs, widespread access to drug susceptibility testing, affordable medicines and a sufficiently sized, well-trained health workforce could address some of those challenges.
BACKGROUND

The last decade has seen remarkable progress in the fight against HIV, tuberculosis (TB) and viral hepatitis C (HCV). Worldwide, new HIV infections have fallen by 37% while HIV-related deaths have fallen by 45% between 2000 and 2018 [1]. Global TB incidence rates declined, on average, 1.6%/year in the period 2000–2018 and the total number of TB deaths declined by 11% between 2015 and 2018 [2]. For HCV, with which an estimated 71 million are infected globally, the introduction of direct-acting antiviral treatments (DAAs) that provide a cure to >95% of individuals infected with HCV with oral regimens of 12 weeks’ duration have stimulated a debate about potential global HCV elimination [3,4]. However, some eastern European countries are continuing to experience challenges to improving healthcare for HIV, TB and HCV. The region reports the highest incidence rate for HIV outside the WHO African region at 44.8/100 000 population, with 111 550 people diagnosed annually [5]. Among the 18 high-priority countries under the ‘STOP TB program in the WHO European Region’ (Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Romania, Russia, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan), the TB incidence rate was estimated at 52.5/100 000, ranging from 13/100 000 in Estonia to 116/100 000 in Kyrgyzstan in 2018 [6]. The eastern European and central Asian countries of the WHO Europe region have the highest proportion of drug-resistant TB among new and previously treated cases of all WHO regions, with an estimated 21% of all new TB patients in the 18 high-priority countries at least resistant to rifampicin [6,7]. In addition, high rates and an increasing prevalence of HIV/TB and HIV/HCV co-infections are reported [8]. Although the alarming dimensions of the syndemics of HIV, drug-resistant TB and HCV have been known for at least a decade, improvement has been geographically variable with most countries only reporting marginal improvements [9-11].

A recent viewpoint in The Lancet has made the case for better integration of diagnostic services for HIV, TB and HCV in eastern Europe and central Asia [12]. Integration of diagnostic services can, however, only be an initial programmatic focus as ending the syndemic of HIV, TB and HCV requires fixing bottlenecks at different stages along the continuum of care, defined as ‘a series of initiating, continuing and concluding care events that result when the patient seeks providers in one or more environments within the health care system’ [4,13,14].

Conceptually, very similar goals along the respective continua of care have been set for the three diseases in the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90–90–90 target; the World Health Organization’s (WHO) End TB strategy and the WHO Global Health sector strategy on viral hepatitis [4,15,16]. Recently, WHO Europe in partnership with other United Nations Agencies published a common position paper on addressing the HIV, TB and viral hepatitis epidemics which, among other measures, commits to ‘increasing and leveraging coordination or integration of services for HIV, TB and viral hepatitis’ [17].

The objective of this article is to provide a comprehensive review of the challenges in healthcare provision for HIV, TB and HCV in eastern Europe. First, we describe the high incidence rates for HIV and the unacceptably high mortality for HIV/TB-coinfected individuals. Then we provide an overview of the challenges and underlying root causes for problems in health care provision to HIV-, TB- and HCV-infected individuals. A particular focus of this review relates to coinfections with HIV/TB and HIV/HCV. Subsequently, we provide a concise overview of the important steps to improve healthcare provision based on our literature review.

SEARCH STRATEGY AND SELECTION CRITERIA

The objective of our search was to identify articles that describe challenges and potential solutions for provision of healthcare to people living with HIV (PLHIV), TB or HCV in eastern Europe. References for this narrative review were identified through searches of PubMed for articles published in English from January 2000, to August 2020, by use of the terms #1, #2, #3 and #4 listed in Box 1. The search strategy was adapted from Dolan et al. [18]. The combination of terms #1 and #4 yielded 3174, the combination of terms #2 and #4 1690, and the combination of #3 and #4 5250 results. After screening of titles and abstracts 37 articles were identified as relevant for this review (Figure 1). Thirty-eight further articles and sources were identified through searches in the authors’ personal files and in Google Scholar. Articles resulting from these searches and relevant references cited in those articles

KEYWORDS

eastern Europe, healthcare, HIV, tuberculosis, viral hepatitis C
FIGURE 1 Flow chart describing the way from the initial findings in PubMed using the search strategy described to those included in the final review article.

BOX 1 Search strategy for PubMed

| Topic | Search string | Articles |
|-------|---------------|----------|
| #1 HIV | #1 HIV [MeSH] OR "Acquired Immunodeficiency Syndrome Virus"[MeSH] OR "AIDS-Related Complex"[MeSH] OR "AIDS-Related Opportunistic Infections"[MeSH] OR "HIV Infections"[MeSH] OR "HIV Seropositivity"[MeSH] OR "AIDS-Related Complex"[MeSH] OR "HIV Seroprevalence"[MeSH] OR "HIV−1"[MeSH] OR "HIV−2"[MeSH] OR "human immunodeficiency virus" [tw] OR "human immune deficiency virus" OR HIV[tw] OR "HIV/AIDS"[tw] OR "HIV-infected"[tw] OR AIDS [tw] | 474 795 results |
| #2 Hepatitis C | #2 HCV "Hepatitis C"[MeSH] OR "Hepatitis C virus" [MeSH] OR "HCV"[tw] OR "Hepatitis C"[tw] OR "liver fibrosis"[tw] OR "viral hepatitis" [tw] | 133 650 results |
| #3 Tuberculosis | #3 Tuberculosis [MeSH] OR "Mycobacterium tuberculosis"[MeSH] OR "Mycobacterium tuberculosis" [tw] OR Tuberculosis [tw] OR "TB"[MeSH] OR "MDR-TB"[tw] OR "XDR-TB"[tw] OR "Mt"[tw] | 260 399 results |
| #4 Eastern Europe & Central Asia | #4 ('Europe, Eastern'[Mesh]) OR 'Asia, Central'[Mesh] | 188 949 results |
| #1 HIV & #4 Eastern Europe & Central Asia | - | 3174 results |
| #2 Hepatitis C & #4 Eastern Europe & Central Asia | - | 1690 results |
| #3 Tuberculosis & #4 Eastern Europe & Central Asia | - | 5250 results |
were reviewed. A limitation of our search strategy is that articles in Russian and other languages without English abstracts were not systematically identified.

RESEARCH ON HIV, TB AND HCV IN EASTERN EUROPE

Although we identified a large number of articles in our initial search, only a few provided original research and data on healthcare provision and clinical outcomes. An additional source is routine surveillance data collected by institutions such as the European Center for Disease Prevention and Control (ECDC). They are an important data source for healthcare planning. However, these national estimates represent an average that covers large differences across key populations and originate from different data sources. To plan differentiated healthcare policy and public health response to HIV, TB and HCV, high-quality disaggregated data are needed for effective interventions that maximize individual health benefits and reduce the risk of onward transmission. The EuroSIDA cohort has, since 1994, collected individual-level data on treatment and outcomes for HIV across Europe [19,20]. This allows direct comparisons of data between countries and detailed subgroup analyses. The TB:HIV study that was initiated in 2011 collects data on patients from 62 TB and HIV clinics in 19 countries across Europe and Latin America (including eastern Europe) to prospectively study the long-term clinical progression of PLHIV with TB [21]. These studies have contributed a central part of the available scientific evidence existing on HIV, TB and HCV from eastern Europe at the individual level [22]. The WHO European Region published in 2019 a TB research agenda based on the input of more than 90 researchers, policy-makers and health practitioners to accelerate and refocus research effort [22]. The strategy outlines the importance of new diagnostic tools, new effective drugs and vaccines and operational research on the high-risk or hard-to-reach population groups [22].

HIGH MORTALITY FOR PEOPLE COINFECTED WITH HIV-TB

In most regions of the world TB is the most common cause of death among PLWH [23]. However, appropriate initiation of antiretroviral therapy (ART) and TB therapy can reduce mortality significantly [24].

In a large cohort study of TB-coinfected PLWH across eastern and western Europe, and Latin America, 1-year mortality was 12%, ranging from 4% in western Europe to 27% in eastern Europe [25]. A likely explanation is insufficient treatment of HIV infection due to low ART coverage and lack of adherence, which in consequence leads to progression of immunodeficiency, reflected in very low virological suppression rates of only 22% compared with 61% in western Europe after 1 year of follow-up [23]. However, it has to be noted that the treat-all policy for HIV and oral treatments for MDR-TB have only become available recently in some of the countries studied.

In eastern Europe TB patients coinfected with HIV are at significantly higher risk of MDR-TB disease than are TB patients without HIV, probably due to shared risk factors such as injecting drug use (IDU) and incarceration [26]. More than a third (39%) of all TB cases among PLWH in eastern Europe are MDR cases [27]. A recent multi-centre study from Latvia, Lithuania, Estonia and the city of Bucharest in Romania reported a median survival of only 5.9 years for patients with unknown HIV status and MDR-TB, pointing out that this was only marginally better survival compared with the pre-antibiotic age in those countries [28].

Globally, MDR-TB treatment success rates for PLWH do not exceed 57% [29]. In PLWH with MDR-TB, 50% died within the first 2 years following initiation of TB treatment in the TB-HIV cohort [26]. Progress was limited compared with a retrospective analysis of data from 2004 to 2006 where 67% of PLWH with MDR-TB had died within 1 year of treatment initiation [30]. Despite the vulnerability of this group, only 13% received ART at baseline, increasing to a maximum of 60% at any time during follow-up, and < 20% of MDR-TB patients had undetectable HIV viral load at any stage during follow-up [23,26]. This is compounded by high loss to follow-up (from both TB and HIV care), ranging from 8% of MDR-TB patients to 19–20% among patients with pan-susceptible TB and those without drug susceptibility testing (DST) [26].

A majority (60%) of deaths in HIV/TB-coinfected persons in eastern Europe were due to TB [25]. The high mortality is probably explained by insufficient ART coverage and virological suppression combined with restricted DST testing and use of inappropriate and failing regimens with few active TB drugs [25]. A healthcare index based on data from the HIV/TB cohort study suggests that DST and at least three active TB drugs, standard TB treatment, early ART initiation and a recent HIV-RNA measurement may improve outcomes for TB-HIV-coinfected individuals [31].
PROBLEM 1: INJECTING DRUG USE AS A COMMON DRIVER OF THE HIV, TB AND HCV SYNDemic

Injecting drug use was first reported as the main driver of the HIV epidemic in eastern Europe more than 20 years ago and at least 50% of all HIV cases could already be linked to this transmission route in 1997 [32]. This proportion is still estimated at 49% in recent EuroSIDA cohort data from the region and compares with 18% in western Europe and 13% in northern Europe [33]. In eastern Europe about 46% of people with recent IDU (PWID) are chronically HCV-infected, compared with 35% globally, and a recent modelling study suggested that up to 96% of new cases in the region could be prevented if IDU transmission was removed [34]. Laws that criminalize PWID and harsh anti-drug policies in eastern Europe and central Asia, in particular Russia, have led to mass incarceration and prison overcrowding with people who inject drugs [35]. In eastern Europe and central Asia, 46% of PLWH received ART [13,43]. Numbers differed widely for countries, from 30% ART coverage in Lithuania to 95% in Uzbekistan [43]. Individual studies based on surveillance data, for instance, from Russia, report even lower ART coverage numbers of around 23%, reiterating the high variability within and between countries [46]. In the TB:HIV cohort covering individual treatment centres, including many university hospitals, PLWH in eastern Europe and central Asia had a higher reported ART coverage, with 72% on ART in 2014, with coverage for individual countries differing from 58% to about 90% [47]. According to data from this cohort, which show ART coverage at 72% in 2015, PLWH in the region have become considerably more likely to receive ART since 2004 (14% in 2004 and 49% in 2009) (Figure 3) [47]. However, the analysis of crude data shows that people in eastern Europe were 17% less likely to receive ART compared with those from western Europe [47]. Further, according to these cohort data, the for coinfection with HIV, TB and HCV, in particular in prisons (Figure 2) [35]. Despite the central role of IDU as a driver of transmission, opioid substitution therapy (OST) was only provided in 43% of clinics in eastern Europe in a recent survey [39]. This is in line with findings of a recent systematic review of interventions to prevent and manage HIV and HCV which found that only 16% of the global population of PWID is receiving OST [40]. In Russia, Uzbekistan and Turkmenistan, OST is still illegal, a major road block to improvement of healthcare for the vulnerable PWID population [41]. In addition, alcohol use disorders are often associated with TB and predictors for worse outcomes, with a particularly high prevalence in countries of the former Soviet Union [42].

PROBLEM 2: HIV LATE DIAGNOSIS AND BELOW TARGET ART COVERAGE AND ART RESPONSE

In 2014, UNAIDS formulated the 90–90–90 target to be achieved by 2020 (90% of all PLWH know their HIV status; 90% of all people with diagnosed HIV infection will receive sustained ART; and 90% of all people receiving ART will have viral suppression) [15]. In 2019, countries in eastern Europe and central Asia reported data against the UNAIDs targets and 76% of all PLWH were diagnosed [13,43]. According to data from the ECDC from 2019 every second HIV diagnosis (50%) in eastern Europe is a late diagnosis (CD4 count < 350 cells/µL or AIDS event at presentation) [44]. Analysis of data from the EuroSIDA and COHERE from 2010 to 2016 found estimated excess AIDS/deaths attributable to late presentation in eastern Europe to be 14 597 (95% CI 10 947–109 680) [45]. In eastern Europe and central Asia, 46% of PLWH were diagnosed with HIV, 46% of PLWH received ART [13,43]. Numbers differed widely for countries, from 30% ART coverage in Lithuania to 95% in Uzbekistan [43]. Individual studies based on surveillance data, for instance, from Russia, report even lower ART coverage numbers of around 23%, reiterating the high variability within and between countries [46]. In the TB:HIV cohort covering individual treatment centres, including many university hospitals, PLWH in eastern Europe and central Asia had a higher reported ART coverage, with 72% on ART in 2014, with coverage for individual countries differing from 58% to about 90% [47]. According to data from this cohort, which show ART coverage at 72% in 2015, PLWH in the region have become considerably more likely to receive ART since 2004 (14% in 2004 and 49% in 2009) (Figure 3) [47]. However, the analysis of crude data shows that people in eastern Europe were 17% less likely to receive ART compared with those from western Europe [47]. Further, according to these cohort data, the
odds of having suppressed viral load in eastern Europe were only 0.16 compared with western Europe in an analysis adjusted for individual characteristics [47]. In eastern Europe 75% of PWID received ART and only 68% of those had a suppressed viral load [33]. It is well known that people with an active illicit drug use usually have particularly poor access to integrated care and harm reduction services in many eastern European countries which underlines that general population coverage and viral suppression rates are likely worse than those found in a cohort study population [33].

The second large, vulnerable population group with below target coverage are PLWH coinfected with TB [48]. At the time point of TB diagnosis, only 17% in this group were receiving ART in eastern Europe in the TB:HIV cohort, despite usually poor immune status. This percentage increased to 54% after 3 months and 69% after 1 year following diagnosis in eastern European countries [23,25]. Patient refusal, which is often due to a lack of medical and social support, was the most commonly reported reason among PLWH for not starting ART by 2 months after the start of anti-TB treatment [49]. This was followed by concerns for toxicity and socio-economic factors such as lack of food or accommodation [49]. In addition, common risk factors for TB/HIV co-acquisition in the region are young age, excess alcohol consumption and imprisonment, which are known to lead to poor treatment compliance and retention in care [49]. In a study from Russia, older age and higher education were associated with retention on ART, while a community-based study from St Petersburg demonstrated that the most consistent predictors of poor care engagement and treatment non-adherence were younger age, male gender, recent substance use, including drinking, drug injection and the use of other illicit substances [46,50]. Furthermore, lower medication-taking self-efficacy (belief in own capacity to adhere to HIV treatment) and lower state anxiety were recorded as predictive of reduced adherence, indicating the important role of social, psychological and medical support in improving outcomes [50].

**PROBLEM 3: INADEQUATE TB DIAGNOSTICS AND TREATMENT REGIMENS**

For TB, the WHO has issued a TB cascade of care in the End TB Strategy which provides targets to be reached by 2025; 90% treatment coverage, 90% treatment success, and 90% new drugs uptake [16]. The countries of the WHO European Region have one of the lowest TB burdens in the world, with 290 000 new TB cases and 26 000 TB deaths reported in the region in 2016 and the number of new TB patients falling faster than the global average (4.3% vs. 1.6%/year) [2,51]. However, up to 20% of new TB cases and up to 70% of previously treated cases are found to be MDR-TB, causing approximately 70 000 cases annually [2,51]. Almost all (90%) MDR-TB cases are found in 18 high-priority countries in eastern Europe and central Asia [7]. The global dimensions of the problem are underlined by the fact that only 3% of the global TB burden is attributable to the region but about 24% of all drug-resistant TB cases are found here [7]. Geospatial analysis revealed that geographical areas in countries of the former Soviet Union with a higher percentage of previously imprisoned TB patients were at greater risk of being MDR-TB hotspots, highlighting the important role of prisons in
sustaining the spread of MDR-TB [52]. According to an analysis of aggregated surveillance data, IDU was even more prevalent as a risk factor for MDR-TB than imprisonment, explaining the high coinfection rates with HCV, TB and HIV in the region (Figure 2) [27,30].

The largest part (81%) of the total burden of the deadly combination of TB/HIV in eastern Europe is located in two large countries in the region: the Russian Federation, with 20% of all TB patients being HIV-positive; and Ukraine, where this is the case for 23% of all TB patients [5]. The particular challenges at the individual level of this vulnerable patient group have been investigated in the TB:HIV cohort [21]. A definitive diagnosis of TB (positive culture or polymerase chain reaction) was provided to about half (47%) of all people, while the remainder were only diagnosed as probable (sputum smear) or presumptive [21]. Anti-TB DST within 1 month of diagnosis was only conducted in 37% of those treated for TB (79% of individuals with a definite TB diagnosis) [21]. Standard TB treatment (including rifampicin, isoniazid and pyrazinamide) was provided to 71%, usually (in 70% of cases) combined with ethambutol (E) and often maintained beyond the recommended 6 months [21]. Only 66% of those with available DST results received an initial regimen of at least three active drugs, despite this being recommended in international guidelines [21]. Furthermore, in 25% of individuals with available DST, treatment included only one or two active drugs, and in 9% no active drugs were included at all in the treatment [21].

About 22% of the TB:HIV cohort in eastern Europe had confirmed MDR-TB, of whom 12% had extensively drug-resistant (XDR)-TB [26]. The PWID were twice as likely and those treated previously for TB were 3.4 times more likely to be diagnosed with MDR-TB [21]. The majority of MDR-TB patients (84%), however, had no history of prior TB treatment or TB prophylaxis [30]. Despite the setting of high MDR prevalence, empiric therapy only provided cover for MDR-TB in 8% of MDR-TB patients, which increased to 44% at 3 months after the TB diagnosis [26]. Approximately 70% of MDR-TB patients received only two or fewer drugs with demonstrated anti-TB activity. Less than 15% received a regimen containing five confirmed active drugs [26].

These findings are in sharp contrast to a recent survey of senior consultants at healthcare facilities in eastern Europe which provided self-assessed access to diagnostics, anti-TB drugs and standards of care [39]. Most clinics (86%) reported routinely performing DST at TB diagnosis, with rapid diagnostic tests such as GeneXpert available in 86% of clinics (up from 54% in 2013) and conventional DST in 57% of clinics [39]. Almost all (92%) eastern European clinics reported using a standardized treatment for drug-susceptible TB and 64% reported a standardized treatment for MDR-TB [39]. Although the availability of rapid diagnostic tests such as GeneXpert reflects progress, it can only detect rifampicin resistance and the high prevalence of MDR-TB calls for rapid genotypic DST beyond just rifampicins.

PROBLEM 4: ABSENCE OF HCV TREATMENT PROGRAMMES

An estimated 11.6 million people are living with a chronic HCV virus infection in eastern Europe [53]. The estimated HCV prevalence across eastern Europe is 3.1%, ranging from 1.3% in Belarus, to 4.5% in Moldova, to 7% in Georgia [53]. The highest rates of new HCV infections (incidence) among ECDC member countries in eastern Europe is found in Latvia, being as high as 59 per 100 000 population [54]. Anti-HCV prevalence is 18%-80% in PLWH and 23%-95% in PWID in eastern Europe [55]. Those coinfected with HIV are a high priority group for higher treatment coverage due to an increased risk of liver fibrosis related to the negative impact of immunosuppression [56]. The WHO Global Health sector strategy 2016–2021 on viral hepatitis aims to provide treatment to 80% of eligible people with chronic hepatitis C virus infection and to reduce HCV-related mortality by 65% by the year 2030 compared with the year 2015 [4]. The key element of the strategy is to ensure the wide availability of DAAs at affordable prices [57]. The latest generation of DAAs achieve HCV cure rates > 95% in both HCV-monoinfected and HIV/HCV-coinfected individuals [58]. The gaps in access to diagnosis and treatment with DAAs, however, are large in eastern Europe with the response in most countries being inadequate [4,59,60]. Taking the estimated regional viraemia prevalence of 2.5% as an indicator for treatment indication, about 6.6 million people are in need of treatment for chronic HCV in eastern Europe (and central Asia) [61]. Reliable and up-to-date data (e.g., surveillance-based) on HCV-DAA treatment coverage in eastern Europe is limited [62]. In eastern Europe, comprehensive data are available from Georgia which has taken the lead in aiming at HCV elimination by negotiating an agreement with Gilead to donate DAAs for 10 years until elimination is achieved [63]. By 2020, the programme has detected, linked to care and treated more than 30% of people with HCV. However, identification and linkage of the remaining 60–70% appear to be a challenge for successful elimination [64].

The EuroSIDA cohort is one of the largest cohorts of HIV/HCV-coinfected individuals in Europe, including eastern Europe [65]. In this observational cohort of a high-risk group, 26% of individuals started any HCV therapy between 2011 and 2016, while uptake of the novel DAA
treatments varied significantly by region [65]. In 2015 and 2016, about 60% of patients undergoing HCV treatment in eastern Europe received DAA-based treatment regimens, compared with more than 90% in western Europe [65]. Although western European countries also reported variable uptake of any form of HCV therapy (range 4–62%), patients in eastern Europe were only half as likely to start treatment (incidence rate ratio = 0.47) [65]. With respect to treatment access, a survey in 2016 found one or more second-generation DAA s registered in 10 (91%) out of 11 surveyed countries in eastern Europe and central Asia [61]. The same survey, however, also found prices for a full-course (12 weeks) generic sofosbuvir treatment, ranging from US$780 in Kyrgyzstan to US$2805 in Ukraine in 2016 [61]. More recently, voluntary licensing agreements of the pharmaceutical companies BMS and Gilead for daclatasvir, ledipasvir, sofosbuvir and velpatasvir have been agreed for Belarus, Ukraine and a number of central Asian countries, and increasing competition is bringing prices down significantly [62]. Russia, the country with the largest absolute number of anti-HCV-positive individuals, however, is not covered by the licensing agreements [62]. A recent analysis of the effect of voluntary licensing for hepatitis C medicines on access to treatment found these agreements to improve HCV treatment uptake substantially, supporting the important role of expansion of licensing [66]. Currently, reliable and up-to-date data on uptake and outcome of HCV-DAA treatment in eastern European countries is urgently needed to assess the epidemiological situation in the region.

**PROBLEM 5: FRAGMENTED HEALTHCARE SYSTEMS**

For more than 10 years it has been clear that integration of healthcare for HIV, HCV and TB, as well as OST and social support for PWID can improve service provision for each of these diseases; increase the detection of TB and HIV; improve medication adherence; the entry and adherence to OST; and decrease the likelihood of adverse drug events [67,68]. This is reflected in the WHO policy on collaborative TB/HIV activities, which recommends integration of HIV/TB services [69]. Several models for integration of healthcare exist, with the ‘one-stop service’ model being one of the most comprehensive [69]. It includes a hospital, TB, HIV or primary care clinic to provide both diagnosis and treatment for both conditions at the same place through the same physician [69]. This can be extended to include OST, HCV diagnosis and DAA treatment [67,70]. A recent review of person-centred care in eastern Europe and central Asia claims that diagnosis and care for TB, HIV and viral hepatitis are separate vertical structures in most countries and therefore need increased political and operational integration to bring them closer to patients [12]. However, for most countries in eastern Europe it is not systematically described what models and attempts at integration are applied [71].

A recent survey of senior physicians providing HIV and TB care in eastern Europe showed that initiation of care for individuals coinfected with both diseases was provided at the same place by the same physician in only 29% of clinics compared with virtually all clinics in western Europe [39]. In the vast majority (79%), care was initiated at special TB hospitals [39]. The testing of all TB patients for HIV was recommended in 85%, while the screening for active TB in all PLWH was recommended in 72% of official national guidelines across Europe [71]. Furthermore, a majority of countries (64%) recommended latent TB infection (LTBI) screening in all PLWH [71]. Provision of care was standardized by relying on national guidelines in all healthcare centres surveyed in eastern Europe, while only 57% of those centres also relied on WHO or European AIDS clinical society guidelines [39]. Systematic follow-up beyond the individual healthcare centre was only reported by 29% of places and no healthcare centre reported standardized adherence support measures [39]. Compared with a similar survey in 2013 no improvement in self-assessed integration of TB and HIV services was observed in eastern Europe [39,72]. Patients were even less likely to be treated for TB and HIV by the same physician and no improvement in the availability of OST was found [39,72]. A slightly positive trend is found for HIV treatment strategies, where earlier initiation of ART regardless of CD4 count is the standard of care in 62% compared with 46% of clinics in 2013 [39,72]. Officially, all countries in Europe now have the treat-all policy [44]. The reality, however, may be even worse than these data indicate as these are self-assessed outcomes where physicians or senior healthcare providers describe the ideal standard of care at their respective healthcare centre.

**CONCLUSION AND NEXT STEPS**

Some eastern European countries face serious challenges to achieve the sustainable development goal-related target of 3.3 by 2030 – among others, to end the epidemics of AIDS and tuberculosis [73]. Furthermore, the current COVID-19 pandemic is adding additional challenges to HIV and TB services globally [74]. Many root causes of these developments, such as poverty, unemployment, imprisonment, mental health challenges, gender inequalities, discriminatory laws, food security and nutrition, and education, are found beyond the health sector and require intersectoral
collaboration [17]. Shortcomings in healthcare provision, however, go a long way to explain the high mortality of HIV/TB coinfections and a rise in MDR-TB and HIV incidence rates. First, IDU has been a driver of the HIV, HCV and, more recently, TB epidemics in eastern Europe and OST is still not broadly established. HIV is diagnosed too late and ART coverage and response to ART in terms of virological suppression are far below the UNAIDS 90% target, in particular in PWID and TB patients. This is despite the fact that the UNAIDS targets were to be reached by 2020; for the next decade even more ambitious fast-track targets do exist, raising the bar for diagnosis, treatment and suppression to 95% [75]. Although, in theory, access to DST and MDR-TB treatment regimens exists, real-life data and outcomes point towards inadequate testing and treatment regimes in TB patients. New HCV-DAA could provide elimination of HCV in high-risk populations (such as PLWH) in eastern Europe but they are not broadly available except for a few notable exceptions. These treatments, though expensive up front, are cost-effective and are found to save money in the long term due to the lower cost of HCV-related complications (e.g. liver cirrhosis) [76].

These challenges are compounded by the absence of integration of care for HIV, TB and HCV. As daunting as this assessment sounds, it also points towards the necessary next steps (Box 2). To address these challenges, healthcare systems need to integrate HIV, TB and HCV services in one place and provide person-centred rather than disease-centred care. Minimal infrastructure requirements are unrestricted OST for all PWID, widespread access to drug susceptibility testing (including GeneExpert and culture-based methods) in combination with affordable (or ideally free at the point of care) MDR-TB drugs and HCV-DAA for high-risk populations. To improve care, standardization based on national guidelines (if necessary, adapted to local factors such as drug resistance) and a sufficiently sized health workforce, trained in HIV and TB care, are needed.

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AUTHOR CONTRIBUTIONS
CK and OK conceived of the article. The original draft was written by CK, AB, DP, AM and OK. LP, AS, JDL and NC contributed topic-specific and local knowledge. All authors were involved in drafting and approving the final manuscript.

ORCID
Christian Kraef https://orcid.org/0000-0002-5224-0335
Adrian Bentzon https://orcid.org/0000-0001-5438-1513
Nikoloz Chkhartishvili https://orcid.org/0000-0002-1309-825X
Daria Podlekareva https://orcid.org/0000-0003-3187-0597

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BOX 2 Important measures to improve healthcare

- Integration of HIV, tuberculosis (TB) and viral hepatitis C (HCV) services in one place, providing person-centred instead of disease-centred care
- Unrestricted opioid substitution therapy for all people who inject drugs
- Widespread access to drug susceptibility testing (including GeneExpert and culture-based methods)
- Affordable (or ideally free at the point of care) multi-drug-resistant TB drugs and HCV direct-acting antivirals for high-risk populations
- Standardization of healthcare, based on national treatment guidelines
- Sufficiently sized health workforce, trained in HIV, HCV and TB care
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