

Syphilis, Hepatitis C and HIV in Eastern Europe

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Abstract

Purpose of review:

Eastern Europe and Central Asia (EECA) has experienced large-scale epidemics of syphilis, HCV and HIV over the past few decades. Here, we review recent evidence on the epidemiology of and the response to these intersecting epidemics.

Recent findings:

The HIV epidemic in EECA continues to expand, with new infections increasing by >50% between 2010 and 2015. HCV is now in the top 10 causes of death in EECA, with Russia accounting for more than half of the global burden of HCV infections, but access to direct-acting antivirals remains a major obstacle for control of the epidemic. Although syphilis incidence is generally declining, high prevalence is reported in key populations, particularly sex workers and people who inject drugs. Recent epidemiological studies have highlighted very high prevalence of HIV, syphilis and HCV in prison populations, alongside poor access to prevention and treatment.

Summary:

Multiple factors are contributing to the ongoing and overlapping HIV, HCV and syphilis epidemics in EECA, including low coverage with antiretroviral therapy and insufficient scale of prevention services. Further research is required to estimate the burden of infections and identify effective prevention and treatment strategies in hard-to-reach key populations, particularly men who have sex with men.

Keywords (3-5):

HIV, HCV, syphilis, epidemiology, Eastern Europe

Word count: 2628 (excluding key points)

Abbreviations:

ART	Antiretroviral therapy
CA	Central Asia
DAA	Direct acting antivirals
DALY	Disability adjusted life year
EE	Eastern Europe
EECA	Eastern Europe and Central Asia
FSW	Female sex workers
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDU	Injecting drug use
MSM	Men who have sex with men
MTCT	Mother-to-child transmission
NSP	Needle and syringe programmes
OST	Opioid substitution therapy
PWID	People who inject drugs
STI	Sexually transmitted infection
TB	Tuberculosis
WHO	World Health Organization

Introduction

Eastern Europe and Central Asia (EECA) is a socioeconomically and geopolitically diverse region that, following the break-up of the Soviet Union, has experienced intersecting epidemics of sexually transmitted infections (STIs) (particularly syphilis), HIV, HCV and tuberculosis (TB), reflecting major socio-economic changes, disruption to public health systems and increased risk behaviours [1-6]. Injecting drug use (IDU) is highly prevalent in parts of the region and has been a key driver of these epidemics [1,2,7]. Eastern and South Eastern Europe has the highest prevalence of IDU in the world, at 1.27% of the population aged 15-64 years, versus 0.25% globally, with almost all the people who inject drugs (PWID) in this region living in Russia and Ukraine [8].

EECA is one of only two regions in the world where HIV incidence is increasing, with new infections increasing by >50% between 2010 and 2015 [9]. This reflects a high proportion of undiagnosed individuals, low treatment coverage (on a regional basis, 21% overall and 31% among those diagnosed [10]) and insufficient and/or ineffective harm reduction and prevention services [11,12]. The latter is especially an issue in Russia, Tajikistan and Turkmenistan which ban the use of opioid substitution therapy (OST) for PWID, and regional coverage of PWID with OST is <1% [11-14].

Our aim is to summarize recent evidence on the inter-related epidemics of HIV, HCV and syphilis in the EECA region (i.e. the eastern part of the WHO European Region).

HIV

Around 90% of people living with HIV in EECA are in Russia and Ukraine, with Russia currently accounting for over 80% of new HIV cases each year [10]. Over half of new infections in Russia in 2014 were in PWID [15]; the contribution of limited harm reduction and poor ART coverage to ongoing HIV incidence in this group is highlighted by recent modelling work, which estimated that coverage of OST, needle and syringe programmes (NSP) and ART at only 14% would reduce HIV incidence by 30% over 10 years among PWID in St Petersburg [16]. Rates of incarceration are very

high overall in EECA, for example 445 per 100,000 in Russia vs median 84 per 100,000 in Western Europe [17], with PWID often incarcerated for minor drug offences resulting in much higher HIV prevalence among prison populations than the surrounding community [11]). A recent Lancet series article explored the central role that prisons play in intensifying and perpetuating the overlapping epidemics of HIV alongside HCV, STIs, TB and substance use disorders in EECA [11]; estimates of HIV prevalence in prisons ranged from <2.5% in Tajikistan and Armenia to 19.4% in Ukraine and 20.4% in Latvia. Recent studies with data on policing and prisons as components of the HIV risk environment in EECA are given in Table 1.

Sexual transmissions, commonly in bridging populations e.g. sex partners of PWID, contribute a substantial proportion of new HIV cases and particularly among women; official figures indicate that 40% of HIV infections in Russia overall in 2014 were heterosexually acquired [15] and 66% in Ukraine in 2013 [26]. Antenatal HIV prevalence is declining in Ukraine (0.33% in 2015) [27] but increasing in Russia (0.75% in 2013 [15]) with around 4000 and 15,000 HIV-exposed infants born each year respectively and mother-to-child transmission rates of 3-4% [28,29]. Intensely discriminatory and punitive legal environments for men who have sex with men (MSM) [30] and PWID [11] in EECA contribute to some misclassification of infections from these groups as heterosexual. A recent study triangulating serosurvey data against MSM population size in Ukraine estimated that only 5% of HIV cases among MSM were correctly classified, with MSM and PWID constituting up to 8% and 35% of the male “heterosexual” category respectively [31]. In Kiev, of 191 men identifying as MSM and accessing HIV testing in 2013-14, a quarter tested positive giving a diagnosis rate of 516-1548 per 100,000, up to 20 times higher than national figures which indicated only 900 infections in MSM up to 2013 [32]. Criminalisation and stigmatisation of MSM are important barriers to coverage of HIV prevention services and HIV testing and treatment in this group [25,30]. A recent randomised trial in 18 MSM social networks in Russia and Hungary assessed a novel sexual risk reduction intervention (i.e. training of network leaders to deliver prevention advice to other members) versus standard

HIV/STI counselling; although there were reduced high risk behaviours and lower incidence of new HIV/STI in the interventional arm (9% vs 15%), statistical significance was not achieved [33].

Clustering of risk factors for HIV among female sex workers (FSW) is well recognised [21,34], with HIV prevalence up to 13-14% among FSW in some regions in Ukraine [26]. Recent data from around 3500 men undergoing HIV testing in St Petersburg and Leningrad indicate a similar clustering of risk in FSWs' clients: history of IDU was independently associated with having sex with a PWID and having purchased sex services [35]. Of the 64% of men in this study who reported not using condoms during last sexual contact, two-thirds had ≥ 1 additional risk factor for HIV acquisition (multiple or casual sex partners, or use of commercial sex worker services). Labour migrants from Central Asia are at high risk of HIV acquisition due to contact with FSW, and are an important bridging population in their home countries [5]; in a recent study among 510 prisoners in Azerbaijan, those who had worked in Russia or Ukraine remained at increased risk of HIV after adjusting for unprotected sex and IDU [23].

AIDS deaths are escalating in EECA, from 38,000 in 2010 to 47,000 in 2015 [9]. This partly reflecting the large "break-points" in the first steps in the cascade of care describing progress towards UNAIDS 90:90:90 targets for 2020 (90% infected diagnosed; 90% diagnosed on treatment; 90% treated with undetectable viral load). In Ukraine in 2015, only an estimated 58% of individuals with HIV were diagnosed and 45% linked to care [9] (56% and 43% respectively in Russia in 2014)[12], and late diagnosis with advanced immunosuppression is common, reflecting poor effectiveness of HIV testing strategies. A study among MSM in Moscow indicated even greater losses in the cascade among this marginalised group, with only 13% diagnosed and 9% linked to care [36]. TB is a major contributor to AIDS deaths due to an epidemic of multi-drug resistant TB, poor ART coverage, poor TB care (including lack of susceptibility testing and use of suboptimal regimens containing <3 active drugs) and late diagnosis of HIV and/or TB with advanced immunodeficiency and disseminated disease [37,38]. A recent study including 834 HIV/TB co-infected people in EE, 317 in Western Europe and

255 in Latin America found that around 40% in EE had multi-drug resistant TB, and probability of death in the 12 months following TB diagnosis was 29% (versus 4% in Western Europe and 11% in Latin America) [38]. Lack of integration of HIV and TB services is an important structural barrier to improvement of outcomes in EE [39,40]. Other service-level barriers to HIV care identified in a qualitative study in Russia related to problems accessing care, dissatisfaction with the quality of services and negative attitudes of healthcare workers [41].

Recent data from a cluster randomised clinical trial among PWID in Ukraine demonstrated the value of peer interventions to reach marginalised high-risk groups, with a peer leader network intervention associated with a 47% reduced hazard of HIV acquisition when compared with standard testing and counselling [42]. Innovative interventions to reach key populations most affected by the HIV epidemic in EE with prevention, testing and treatment services are urgently needed. However, services for HIV-positive people and particularly PWID in Ukraine have been severely disrupted by the recent conflict, in which >1.7 million people had been displaced [43], healthcare services interrupted [28] and OST programmes abruptly halted in occupied territories [44,45].

Hepatitis C

EECA is among the global regions with the highest HCV infection rates. An estimated 6.6 to 9.5 million people live with viraemic infection in the region [46,47], accounting for 2.3% prevalence among general populations, twice as high compared to global estimates (Table 2). The epidemic is diverse in the region with HCV viraemia ranging widely from 0.9% in Belarus and 1.7% in Latvia to 4.4% in Uzbekistan [47]. Russia has the highest absolute number of infections and is one of the six countries in the world (together with Egypt, China, India, Nigeria and Pakistan) accounting for more than half of the global burden [47].

The recent Global Burden of Disease Study estimated global mortality attributable to viral hepatitis has increased since 1990 [48]. In 2013 alone, HCV accounted for over 38000 deaths and over a

million of disability adjusted life years (DALYs) in EECA (Table 2), and became the 10th and the 4th leading cause of death in EE and CA respectively [48,49].

The most common genotype in the region is 1b, accounting for two-thirds of all infections ranging from 53.5% in Belarus to 87.7% in Latvia; it is followed by genotype 3 with a wide range from 7.7% in Tajikistan to 38.5% in Belarus [47,49]. There is some data showing that genotype 3 is more common in PWID in Russia, with genotype 1b more common in the general population and in dialysis patients [50].

IDU is a major driving force for the HCV epidemic in EECA. PWID have estimated HCV-seroprevalence ~20 times higher than the general population, accounting for 1.5 million people with chronic infections in the region [46]. In Russia, Ukraine and Georgia, HCV seroprevalence in PWID as high as 71-90% were reported, accounting for 22-40% of the total HCV burden in these countries [51]. With the highest rate of incarceration of PWID and other at risk groups [11], EECA has one of the highest estimated HCV seroprevalence in prisoners at 20.2% (95%CI 11.8-30.1)[52]. However, recent studies in prisons have reported even higher HCV seroprevalence in some countries (Table 1).

Other key populations at high risk are MSM and sex workers with an estimated HCV-seroprevalence nearly twice and five times as high as in general population respectively [46]. No recent studies on HCV seroprevalence in MSM in EECA have been published; in a 2013 publication, HCV seroprevalence was 4.5% in a biobehavioural surveillance study in Moldova [53].

Access to testing and treatment remains a major obstacle for control of the HCV epidemic in EECA. New direct-acting antivirals (DAAs) with over 90% cure rates and minimal side-effects provide a great promise, but costs remain prohibitive, particularly for middle-income countries with no access to generic drugs. In a recent review, estimated treatment uptake in 2013 ranged only from 0.1 to 0.5% among the general HCV viraemic population [51]. PWID remain largely excluded from national programs [54], despite being the most affected population and the most cost-effective group to treat [55]. In Russia, Ukraine and Georgia, PWID accounted for <1%, 10-20% and 20-30% of all

treated persons respectively [51]. Martin et al, in their modelling analyses showed that treatment of PWID with DAAs in conjunction with high-coverage NSP and OST can substantially reduce HCV prevalence in the general population [55,56]. Regionally, there is no HCV treatment provided in prisons, with the exception of Georgia [11].

HIV-HCV Coinfection

Overlapping transmission routes for HIV and HCV explain the high rate of HIV-HCV coinfection in EECA with the highest HCV prevalence in HIV-infected PWID (median 83%, IQR 56–98%)[57]. Recent estimates suggest that EECA accounts for 27% of the global burden of co-infection (median 607,700 co-infected persons, IQR 404,100–746,500)[57]. Data on HIV-HCV coinfection prevalence in populations other than PWID are limited in EECA, particularly for MSM. A recent study of around 1500 childbearing women (recently delivered) with HIV living in Ukraine reported that 33.5% had HCV co-infection, with 20% reporting an IDU history [58].

Co-infection leads to accelerated progression to final stages of liver disease, hepatocellular carcinoma and increased mortality [59], with a profound impact in EECA where access to treatment of both infections is challenging, especially for key populations. In a recent study of HIV/HCV co-infected children and young people from across Europe, among those from EE, only 31% had been treated with pegylated interferon/ribavirin (6/67 in Ukraine and 30/49 in Russia) and less than 50% achieved sustained virological response [60]. Ukraine is a notable exception, where a recent project launched by International HIV/AIDS alliance aims to treat 1500 patients from most vulnerable populations, including PWID, PWID HIV-infected partners and commercial sex workers, with sofosbuvir-based regimens. They showed excellent retention in care and adherence to treatment and high rates of successful outcomes in the initial stage of the project [61].

Syphilis

EE includes some regions that historically were hyper-endemic for syphilis, but syphilis incidence has been declining following the major epidemic in the 1990s [3]. A recent analysis of Russian data showed that incidence declined nationally from 79.4 per 100,000 in 2004 to 28.9 per 100,000 in 2013, but remains high in some regions, particularly the Far Eastern, Siberian and Northwestern Federal districts [62]. These declines in Russia are occurring against a backdrop of increasing syphilis incidence in the EU/EEA, mainly driven by MSM, although even the highest incidence countries have considerably lower rates than Russia (e.g. 7.2 and 7.7 per 100,000 in UK and Spain respectively)[63].

The first molecular epidemiological study of syphilis in EE was recently conducted, in the Tuva Republic, in southern Siberia: the authors estimated an incidence rate of 177 per 100,000 in 2013 and demonstrated that the 14d/f *T.pallidum* strain caused 91% of the syphilis cases [64]; this study also reported a 2.4% prevalence of macrolide-resistance (23S rRNA A2058G). A recent report from the Czech Republic has documented a substantial increase in macrolide-resistant strains (A2058G and A2059G 23S rRNA) over time [65,66], consistent with findings from elsewhere in Europe and globally [67].

Knowledge of syphilis epidemiology depends on the national STI surveillance systems, which may incorporate case reporting by STI centres, monitoring of syphilis prevalence in pregnant women, congenital syphilis monitoring and bio-behavioural surveillance surveys in key populations. Recently published incidence and prevalence data for the general population, as well as for key populations are presented in Table 3. These systems may also monitor the proportion of early (i.e. primary, secondary and early latent syphilis) versus late (i.e. late latent and tertiary syphilis) cases. In Russia, an increase in the proportion of late forms of syphilis has been reported, from 1.2% in 2004 to 12% in 2013 [62]. This is of concern, as it may indicate issues with access to testing and treatment.

Elimination of vertical transmission of syphilis was launched as a global target by the WHO in 2007 (alongside that for HIV). Maternal and congenital syphilis rates have declined, although in 2012 there were an estimated 102,000 new congenital infections worldwide [75]. A recent WHO Europe regional technical consultation noted that barriers to elimination of congenital syphilis in EE include poor access to antenatal care for women in key populations and unnecessary delays between antenatal diagnosis and treatment [76]. In June 2016, WHO validated elimination of MTCT of syphilis in Belarus and Moldova (i.e. $\geq 95\%$ antenatal care coverage, $\geq 95\%$ antenatal syphilis testing coverage, $\geq 95\%$ treatment of seropositive women achieved over ≥ 2 years, plus incidence of congenital syphilis ≤ 50 cases per 100,000 livebirths achieved for ≥ 1 year)[77].

Conclusion

The HIV, HCV and syphilis epidemics have highlighted the frailties of health care systems in EECA, and widespread stigma, denial and neglect of health problems of key populations. Screening, treatment and prevention strategies, focused on regional risk factors, need to be significantly strengthened as an estimated 2 million Russians will be HIV-positive by 2020 based on current trajectories. Progress towards the WHO target of eliminating HCV as a public health problem in the next 15 years and the UNAIDS 90:90:90 target by 2020 will only be possible with strong advocacy, political commitment, substantial financial investments and improvements in social justice and equity.

Key Points

- The burden of HIV, HCV and syphilis infections in Eastern Europe and Central Asia is high, and partly reflects the high prevalence of injecting drug use in the region, with HIV and Hepatitis C among the 10 top mortality causes in the region
- Stigma and discrimination around these infections and the associated key populations (e.g. MSM, PWID, sex workers) are important barriers to access to care, treatment and prevention
- The proportion of people living with HIV on antiretroviral therapy is one of the lowest in the world, whilst access to new directly acting antivirals for treatment of HCV is challenging due to prohibitive costs for low-middle income countries, as most in EECA are excluded from voluntary licences
- The region's prisoners have amongst the highest HIV and HCV prevalence worldwide among incarcerated populations. Access to diagnosis and treatment for both infections and OST in prisons is largely non-existent or inadequately scaled to need.
- Data on prevalence of HIV, HCV and syphilis in MSM and sex workers are very limited

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Conflict of interest

The authors have no conflicts of interest.

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