European AIDS Treatment Group

EACS European AIDS Clinical Society

Meeting report:
Standards of care for HIV and coinfections in Europe

Summary report:
High-level Ministerial Meeting on HIV

November 2014, Rome, Italy

Meeting report: Standards of care for HIV and coinfections in Europe

Organised by the European AIDS Clinical Society (EACS) in collaboration with European AIDS Treatment Group, under the auspices of the Ministry of Health, Italy.

25-26 November 2014, Rome, Italy

Introduction

The aim of the international meeting, *Standards of care for HIV and coinfections in Europe*, was to gather information on HIV and hepatitis clinical care in Europe. In particular, the meeting focused on late presentation to care, access to care and to HIV treatment, retention in care both in Western and in Eastern European countries, reviewed current trends and management of chronic hepatitis B and C, as well as HIV and hepatitis C co-infection and HIV and tuberculosis in Europe.

The expected outcome is to have a complete picture of HIV and hepatitis care in order to identify critical areas of intervention, recognise the future challenges in screening, monitoring and diagnosis of people with HIV, hepatitis C or hepatitis B, integrating the latest scientific results to improve the quality of life of people with HIV and hepatitis in Europe.

Natural history, epidemiology and late presentation in the European region

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Epidemiology
An estimated 2.4 million people (range 2.1–2.7 million) are living with HIV in the World Health Organization (WHO) European region, of whom 1.5 million live in Eastern Europe. In 2010, 76% of all new HIV diagnoses in the region occurred in Eastern Europe, 90% of these in Russia and Ukraine. Three countries (Estonia, Russia, Ukraine) reported >20 HIV infections per 100,000 inhabitants. Whereas the number of people living with HIV has doubled in Western and Central Europe since 1990, it has more than tripled in the past decade alone in Eastern Europe, the only region in the world where HIV incidence continues to rise. In 2010, 43% of new infections in Eastern Europe were reported as due to injecting drug use, compared to 4% in Western Europe.

Late presentation of HIV disease in the European region
Late presentation for HIV care and treatment increases the risk of mortality, prolongs the period during which transmission risk is high, reduces the risk of viral suppression on treatment and is associated with higher risks of non-AIDS events, drug-drug interactions and hospitalisation. Late presentation is also associated with substantially increased health care costs due to increased morbidity and hospitalisation.(1) A European consensus definition of late presentation was adopted in 2009, consisting of:

- Late presentation: Persons presenting for care with a CD4 count <350 cells/mm^3 or presenting with an AIDS-defining event, regardless of CD4 cell count.
- Late presentation with advanced disease: Persons presenting for care with a CD4 count <200 cells/mm^3 or presenting with an AIDS-defining event, regardless of CD4 cell count.(2)

Longitudinal cohort data show little change in late presentation over the past decade.(3)

Changes in the natural history of HIV disease over the past 20 years in European cohorts indicate a higher viral load set point in men who have sex with men, and lower CD4 cell counts after seroconversion, implying that individuals acquiring HIV today reach a CD4 cell count of 500 within 2.5 years of infection, compared to an interval of 4 years, 20 years ago.(4) The viral load set point in seroconverters increased by approximately 0.5 log between 1990 and 2008, indicating a 44% increase in HIV transmissibility in individuals not receiving antiretroviral treatment.(5) Taken together, these findings suggest that individuals acquiring HIV today may be more likely to transmit HIV and are in more rapid need of antiretroviral treatment, indicating the need for improvements in the coverage and frequency of HIV testing in key populations in order to minimise late presentation.

HIV testing

Prof. Amanda Mocroft, University College London School of Medicine, UK; Dr Deniz Gökingen, Ege University, Izmir, Turkey; Nikos Dedes, European AIDS Treatment Group, Greece; Tamás Bereczky, European AIDS Treatment Group, Hungary.

The lack of change in late presentation suggests that improving the coverage of voluntary counselling and testing will not have a substantial effect, and that provider-initiated testing and counselling strategies will need to be expanded to reach those currently untested. A number of settings offer opportunities to target the offer of an HIV test to those at high risk of exposure, including genitourinary medicine clinics, TB clinics, drug dependence clinics and antenatal care, together with the expansion of community-based screening for men who have sex with men and people who inject drugs. Indicator-condition guided

HIV testing also has the potential to identify undiagnosed individuals at high risk of presentation with advanced disease. A multicentre European study of indicator-condition guided testing (HIDES II) in 42 clinics in 20 European countries in 9471 adults aged 18-65 found an overall prevalence of 2.5%. The study identified 10 conditions associated with an HIV prevalence > 0.1% (the level judged to be cost-effective for provider-initiated screening).(6)

HIV indicator conditions associated with HIV prevalence > 0.1%	
Hepatitis B and C dual infection:	9.6%
Mononucleosis:	5.3%
Lymphadenopathy:	4.4%
Leukocytopenia:	4%
Pneumonia:	3.2%
Neuropathy:	2.4%
Hepatitis C:	2.3%
Dermatitis:	2%
Hepatitis B:	1.2%
Cervical cancer:	1%

The uptake of HIV testing is likely to be improved across all settings by expanding the availability of testing beyond clinical settings and by the use of high-quality rapid antibody testing. Targeted campaigns have been shown to increase the uptake of testing. Provider-initiated testing in a range of clinical settings has been shown to increase coverage and yield of antibody testing. HIV testing services should provide good linkage to HIV care and treatment together with ensuring confidentiality and non-discriminatory care.(7) New guidelines on HIV have been published by the International Union Against Sexually Transmitted Infections for use in genitourinary settings and primary care where treatment for sexually transmitted infections (STIs) might be provided.(8) The guidelines were developed to address the diversity of practice and health system organisation in the European region, including the absence of national guidance on HIV testing in some countries. Historic guidelines on HIV counselling and testing may have emphasised the negative consequence of an HIV diagnosis at the expense of communicating the benefits of early diagnosis and treatment. The 2014 guidelines recommend HIV testing for all who present for genitourinary care as part of initial screening, and for all patients presenting to primary care who report a high likelihood of HIV exposure. Annual testing is recommended, with more frequent testing recommended where an ongoing risk of exposure is reported. Improvement in testing frequency requires a dialogue between doctor and patient and the development of a trusting relationship that allows the patient to disclose ongoing risks for HIV exposure.

The guidelines strongly emphasise the use of fourth-generation HIV p24 antigen/antibody assays. These tests reduce the window period to approximately six weeks. Confirmatory algorithms vary but national guidelines for use always recommend at least one confirmatory test using a different assay. In cases of suspected primary infection where serology is negative, HIV RNA testing should be used in preference to a nucleic acid amplification test (NAAT). The guidelines also consider the use of point-of-care tests using blood or oral fluid, whether conducted by a health care worker or by self-testing. The guidelines note a reduction in sensitivity in early HIV infection and when used with samples other than blood.

A major barrier to the implementation of new guidance regarding HIV testing is a lack of training and awareness among health care providers, especially among non-HIV specialists.

Key discussion points

- EACS should consider whether guidance on testing should form part of its portfolio of clinical guidance.
- Health care providers should be encouraged to ask patients for more information about their HIV testing history.
- More information is needed about successful models of community HIV testing, and these models need to be resourced at national level in order to expand the coverage of HIV testing among key populations.

Overcoming barriers to HIV testing

A high proportion of people living with HIV remain unaware of their infection: the proportion who remain undiagnosed ranges from up to 20% in Denmark, Sweden and Slovakia, and 30% in the United Kingdom, France and Germany to at least 50% in Poland and Latvia. Heterosexual men, older people, migrants and people living in areas with low HIV prevalence are more likely to remain undiagnosed. By exposure category, heterosexual people from sub-Saharan Africa are more frequently diagnosed late than any other group in the European Union (61% in 2012).(9)

Barriers to HIV testing

Patient	Provider	Structural
• Low risk perception • Lack of awareness of HIV and treatment availability • Fear of HIV infection and its health consequences • Fear of disclosure (worries about stigma, discrimination and rejection by significant others) • Denial • Difficulty accessing service, especially migrant populations	• Patient not perceived to be at risk • Insufficient time • Burdensome consent process • Lack of knowledge/ training • Stereotyping – fear of appearing to discriminate • Pretest counselling requirements • Reimbursement issues or lack of reimbursement incentive In Eastern Europe also: • Corruption, including payments to health care providers for services • High prevalence of discriminatory attitudes towards key populations, sanctioned by authority	• Lack of national policy on HIV testing • Lack of services that are friendly to key populations e.g MSM, drug users, Africans • Regulatory and licensing systems that prevent all health care providers from offering a test • Medical device regulations that prevent use of point of care tests • Lack of anti-discrimination laws • Criminalisation of people who inject drugs, sex workers and men who have sex with men In Eastern Europe also: • Weak NGO sector • Lack of political pressure to provide HIV services • Political opposition to key populations at all levels • Widespread non-adherence to international guidance and standards of good practice

In Eastern Europe, barriers to HIV testing need to be considered in the context of differences between health systems and an extensive history of authoritarian and normative control of individual behaviour and autonomy at the state and clinical levels.

Potential solutions

- Mass media campaigns can have an impact on testing behaviour in the short term.
- Reducing stigma around HIV testing and diagnosis can be addressed at the institutional level through ‘normalisation’ of the testing procedure and the introduction of a universal offer of testing.
- Training healthcare providers can effectively increase HIV testing rates and improve healthcare providers’ attitudes towards HIV and confidence in conducting a test.
- Written informed consent has been identified as a barrier to testing, verbal informed consent is an acceptable alternative and results in higher testing uptake.
- Brief post-test information may be given to those testing negative in place of counselling.
- Local strategies work better.
- Community based testing should be part of an overall, reasonable testing strategy.

Key discussion points

- Importance of developing local models and disseminating information about successful local models, rather than importing models from other health systems that may not be easily adaptable to local circumstances. Demonstration projects need to be funded and evaluated.
- Increase partnerships between the community and health care providers at all levels
- Increase dissemination of information about current guidance on HIV testing and best practice in HIV testing in multiple languages, especially Russian.
- Engage with specialist societies regarding indicator diseases in order to promote HIV testing to their members at a

European and national level.
- Increase pressure for targeted surveillance that will provide more accurate data on local HIV prevalence and prevalence in key populations, in order to influence policy development and risk assessment in clinical practice.
- Greater focus on provision of testing services for key populations is needed, especially in Eastern Europe, together with stronger provisions to protect confidentiality and human rights.
- In low- and high-prevalence settings, it is important to create a culture of confidentiality among health care staff and service users so that people can use testing services and HIV clinics without fear of disclosure.

Improving access to antiretroviral treatment

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Antiretroviral treatment has led to greatly enhanced life expectancy among people living with HIV and has reduced the burden of morbidity and mortality in all regions. Higher treatment coverage at a national level has been associated with a reduction in HIV transmission.(10) UNAIDS has endorsed a new post-2015 target for antiretroviral treatment coverage that recognises the importance of achieving high levels of HIV diagnosis, linkage to care and viral suppression in order to reduce HIV transmission, morbidity and mortality. The new target seeks to diagnose 90% of people living with HIV, ensure that 90% of those diagnosed receive antiretroviral treatment and ensure that 90% of those on treatment have fully suppressed viral load. If this target can be achieved by 2020 it would result in 90% of people living with HIV diagnosed, 81% on treatment and 73% with fully suppressed viral load.

The European region is falling behind countries where innovative approaches to the delivery of testing and treatment, coupled with high-level political commitment, have resulted in high levels of treatment coverage despite limited domestic resources for health.

Antiretroviral treatment in Eastern Europe
A survey of treatment access in Eastern Europe and Central Asia carried out on behalf of EACS by Cristiana Oprea found substantial differences within income bands in the region in treatment coverage, regimen availability and continuity of drug supplies.

Key findings from lower middle income countries
With the exception of Ukraine, countries in this income band have low HIV prevalence and in most cases are highly reliant on support from international donors to provide antiretroviral treatment. HIV epidemics appear to be concentrated in people who inject drugs and heterosexuals. Antiretroviral coverage is low, typically less than 20%, and treatment is provided by infectious disease specialists. Preferred antiretroviral regimens follow EACS or WHO guidelines in almost all cases, but single-dose combinations and newer antiretroviral products remain unavailable. Ukraine is the major exception: 47% of patients on first-line treatment are receiving a nelfinavir-based regimen (nelfinavir is a non-boosted protease inhibitor withdrawn from the market in Europe in 2008, and no longer recommended in any international guidelines). Stock outs of antiretroviral products have occurred in the past two years in most countries in this income band.

Key findings from upper middle-income countries (including central and south-eastern Europe)
All countries in this income band have very low HIV prevalence (<0.1%). Varied concentrated epidemics are present in upper middle-income countries in the region, among men who have sex with men (MSM) in Hungary and Serbia, and among people who inject drugs in Azerbaijan and Romania. Antiretroviral treatment (ART) initiation is recommended at 350 CD4 cells/ mm^3, although Hungary and Romania have moved to ART initiation at 500 CD4 cells/ mm^3. ART coverage varies from 30% in Kazakhstan and 45% in Belarus to 69% in Romania. Preferred ART regimens largely reflect EACS guidelines, although recommended regimens are more limited in South Eastern Europe. Newer agents and single-dose combinations are unavailable in most countries. Stocks outs have been reported in the past two years in Albania, Macedonia, Serbia and some regions of Romania.

Key findings from higher-income countries (Russia & Central Europe)
HIV prevalence is low in higher-income countries with the exception of the Russian Federation (1%). HIV prevalence is high among people who inject drugs in Russia and Poland, and among MSM in Croatia, Czech Republic and Slovakia. ART initiation is recommended at 500 CD4 cell/ mm^3, except in Russia, where ART initiation is recommended at 200 CD4 cells/ mm^3. ART coverage is equivalent to Western European levels (>60%) in all countries except Russia (20-34%). Preferred ART regimens follow EACS guidelines, although information was unavailable for Russia. Newer agents and single-dose combinations are available and preferred in first-line treatment in most countries. Only Russia has reported ART stock outs in the past two years.

Antiretroviral treatment in Western Europe
Current EACS guidelines recommend treatment for all patients with CD4 cell counts below 350, and recommend that treatment should be considered for patients with CD4 cell counts in the range 350-500. Pending the results of a randomised clinical trial of early ART initiation, observational cohort data provide inconsistent evidence about the effect of early ART initiation on morbidity and mortality. A higher CD4 cell count at ART initiation is associated with a greater likelihood of CD4 cell count normalisation,(11) and the duration and magnitude of uncontrolled viremia (viral load copy years) is associated with an increased rate of AIDS-defining events.(12) Viral suppression was associated with an extremely low risk of transmission to sexual partners in the PARTNER cohort study, emphasising the preventive benefit of treatment at any CD4 cell count.(13)

Prescribers of ART face growing budgetary pressures in many European settings to limit overall expenditure on ART and to consider the costs of individual agents. Cost effectiveness analysis has identified abacavir, lamivudine and efavirenz to be more cost-effective in the Spanish health system than tenofovir, emtricitabine and efavirenz or tenofovir, emtricitabine and rilpivirine.(14) The introduction of generic antiretrovirals upon the expiry of patents between 2014 and 2018 is likely to force further consideration of costs when prescribing.

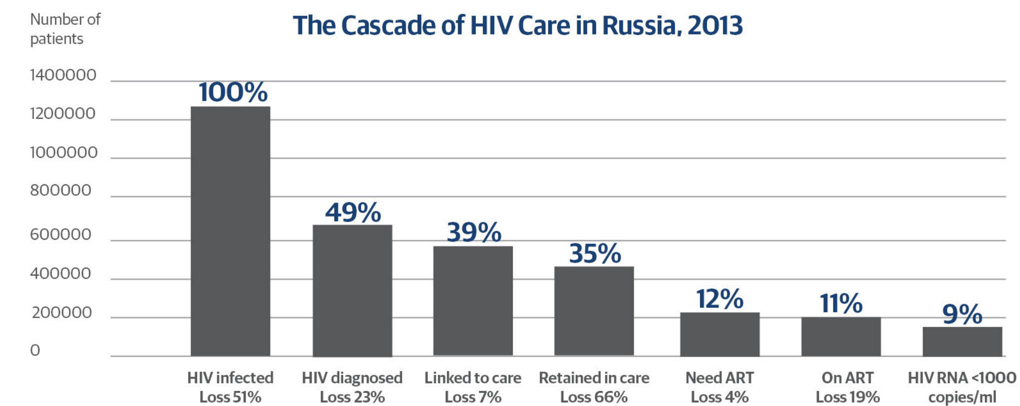
Improving retention and quality of care

Prof. Cristina Mussini, University of Modena, Italy; Prof. Jens Lundgren, University of Copenhagen, Denmark.

Comparative treatment cascades in high income countries (15)

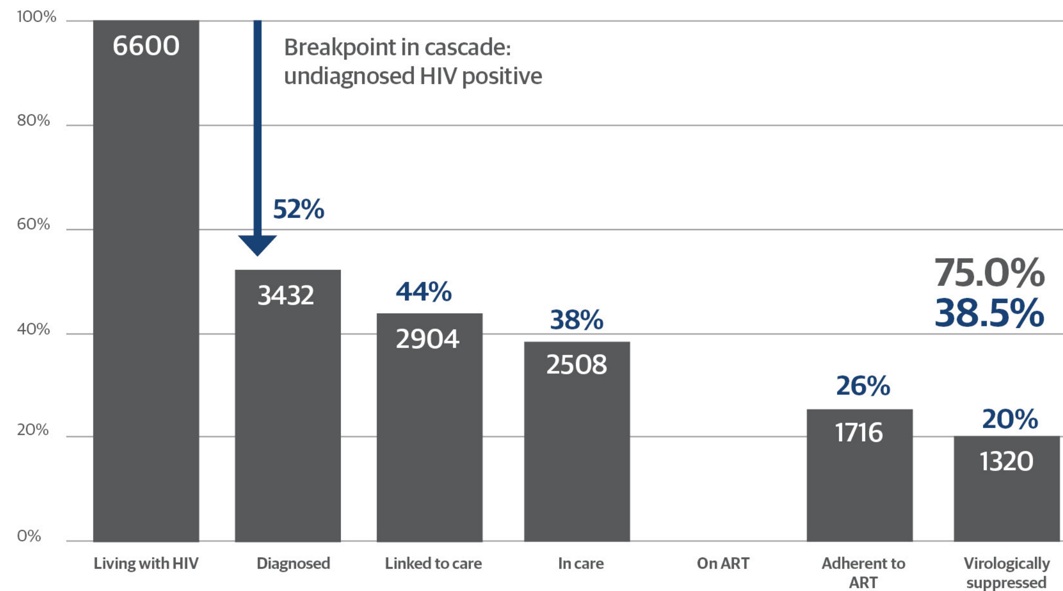
	Living with HIV	Diagnosed	Linked to care	In care	On ART	Adherent	<50
Australia	27,674	86%	78%	76%	66%		62%
Denmark	6,500	85%	81%	75%	62%		59%
United Kingdom	98,400	n/a	79%	70%	67%		58%
Netherlands	25,000	n/a	73%	68%	59%		53%
France	149,000	81%	n/a	74%		60%	52%
Canada (BC)	72,000	71%	67%	57%	51%	44%	35%
United States	1,148,000	82%	66%	37%	33%		25%

Note: discrepancies in data provided indicate differences in national surveillance criteria. For Canada, the cascade percentages used are taken from a study in British Columbia, and have been applied to the numbers of people living with HIV in Canada as a whole.



Despite weakenesses in HIV diagnosis, very high rates of viral suppression are being achieved in patients diagnosed and retained in care in Western Europe; evidence from Italy indicates that being on antiretroviral treatment was associated with a significantly reduced risk of non-retention in care, whereas migrants were at high risk of non-retention in care. Language and cultural barriers and the pressures of economic recession make it more likely that migrants will be lost to follow up or forced to move to seek work. Migrants represented 40% of HIV diagnoses in the European Union between 2007 and 2011, 92% of these

in Western Europe.(16) In Eastern Europe, a lack of targeted testing for key populations together with stigma and discriminatory laws result in low rates of diagnosis. Lack of awareness of HIV, lack of awareness of treatment, highly restrictive treatment eligibility criteria and limited availability of treatment for financial reasons each contribute to the very low rates of viral suppression observed in Eastern Europe.



Improving the quality of HIV care in Eastern Europe could avert at least 80,000 deaths a year. A focus on essential elements of care is required: provision of antiretroviral therapy and treatment of tuberculosis according to current international guidelines is essential and treatment for hepatitis B and C is important. Screening and management of lifestyle-related comorbidities and organ dysfunction is also desirable according to the level of resources available. This represents a public health approach.

People who inject drugs need models of care which can address all their health needs at one site rather than models of care which require them to navigate multiple vertical services providing treatment for drug addiction, HIV, general medical care and TB. Many drug users find it difficult to maintain steady relationships with multiple health care providers and need access to community-based services which provide care through collaboration of an expert team. Numerous models of shared care for people who inject drugs have been developed in Western Europe and the shared care model is recommended by the World Health Organization.

Opioid substitution therapy (OST) is an especially important element of care for people who inject drugs. It contributes to improved retention in care by stabilising problematic drug use and engaging drug users with health care services. The proportion of people who inject drugs receiving OST is extremely low in most Eastern European countries (<5% in Russia, Belarus, Ukraine) compared to Western Europe (50-60% in United Kingdom, Netherlands, Italy).

In Western and Central Europe, the successful expansion and simplification of antiretroviral therapy has resulted in a large population of patients who are stable on long-term ART. Approximately 70% of cohort participants on ART in the region had fully suppressed viral load on the same regimen for at least 12 months in 2013 (compared to approximately 40% in Eastern Europe). The improved stability of health among a growing population of people living with HIV implies a need for less frequent clinic visits, decentralisation of some elements of care to general practitioners and the need for models of task shifting to nurses and specialist pharmacists. However, one size will not suit all, and as HIV care is restructured to accommodate changes in the HIV population and budgetary pressures, it is important that quality is not compromised and that flexibility to address the evolving needs of an ageing cohort is retained. HIV specialists need to remain in overall charge of patients but electronic record-keeping and decision-management systems, together with electronic unique identifiers and community follow-up of patients lost to care, can support decentralisation of care while optimising retention.

Strategies for improvement of care in Eastern Europe

- EACS and other professional groups have an important role to play in health diplomacy between the European Union and Eastern European states.
- Greater engagement with health care professionals in the region through invitations and support to international meetings will facilitate discussions with peers on best practices.
- It took a number of years to gain acceptance for harm reduction practices in Western Europe, so we need to be persistent in expert dialogue.
- Countries that may be close to some Eastern European countries in political culture (e.g China, Vietnam) have adopted harm reduction policies in recent years. What can be learnt from these policy shifts and how can these countries be engaged in supportive expert dialogue at the scientific and political levels?
- Political dialogue will be essential in order to ensure political leadership in Eastern Europe. G8-level Health Minister support, and dialogue between multilateral agencies and Health Ministries, will continue.
- In lower prevalence countries, EACS has an important role to play in raising standards through training, research networks and in-country visits, and by advocating good practice through engagement with Health Ministries, who may be unaware of recent guidance.

Coinfections

HIV and tuberculosis

Dr Enrico Girardi, National Institute for Infectious Disease L Spillanzi, Rome, Italy; Dr Daria Podlakareva, University of Copenhagen, Denmark.

Tuberculosis notification rates were five to ten times higher in Eastern Europe than in Western Europe in 2012 and an alarming proportion of newly diagnosed cases are multi-drug resistant (32-35% in Belarus in 2010-2012 and 14.4% in Russia in 2010).(17-19) A regional comparison of TB treatment in people living with HIV between Eastern Europe and Western Europe, Southern Europe and Latin America showed that patients were more likely to be treated presumptively for TB in Eastern Europe than other regions and less likely to undergo diagnostic procedures including drug susceptibility testing than in Western and Southern Europe.(20) Among those who underwent drug susceptibility testing in Eastern Europe, 40% had multidrug-resistant TB compared to <5% in Western Europe, and 64% of patients who underwent drug susceptibility testing received treatment with four active drugs, as recommended by WHO. Similarly, inter-regional comparison has shown mortality from TB in people living with HIV was substantially higher in Eastern Europe than in the rest of Europe (33% vs 8-14% at 12 months).(21) The elevated risk of death from TB among people living with HIV in the region is strongly associated with multi-drug resistance and disseminated disease.(22) Regional variations in TB treatment practice and delivery are likely to contribute to these poor outcomes, especially inpatient hospitalisation during the intensive induction phase (increasing the risk of nosocomial transmission), lack of opioid substitution therapy leading to poor adherence among drug users, lack of integration between HIV, TB and narcology services, a limited formulary of drugs for second-line TB treatment and lack of drug susceptibility testing.(20) Consensus discussion identified the following priority measures needed to reduce the burden of TB in people living with HIV in the region:

- Consistent implementation of best practice in infection control in TB and HIV settings, and intensified case finding among key populations
- Availability of rapid TB diagnostic and drug susceptibility tests for TB
- Adequate empiric TB treatment and subsequent TB re-treatment guided by results of drug susceptibility testing
- Unlimited availability of all TB drugs, especially newer products such as bedaqualine, and development of shorter treatment regimens
- Adequate treatment of HIV infection and unlimited ART coverage
- Need for experts to support evidence-based drug policies that include a recommendation on the use of buprenorphine or forms of OST other than methadone (due to drug-drug interaction with rifampicin)
- Improved surveillance and political will to act on the basis of data and public health needs

Hepatitis C & HIV coinfection

Dr Antonella d'Arminio Monforte, University of Milan, Italy; Dr Karine Lacombe, Hôpital St Antoine, Paris; Dr Sanjay Bhagani, Royal Free Hospital, London, UK.

Hepatitis C prevalence in people living with HIV is associated with a history of injecting drug use, previous residence in countries with high hepatitis C virus (HCV) prevalence, a history of exposure to blood products prior to 1991, and more recently with sexual exposure among men who have sex with men (MSM). HCV antibody prevalence among people living with HIV is highest in Eastern Europe (57%), Central Europe (34%) and Southern Europe (28.8%) and is highly concentrated in urban populations.(23) Genotypes 1 and 3 are the most prevalent forms (53% and 29% respectively) in coinfected people. (24, 25) HCV prevalence among people who inject drugs has declined over time but an epidemic of HCV in MSM associated with unprotected sex, group sex and injection of stimulants has emerged in Western Europe.(26, 27) Screening for HCV

in coinfected people remains variable despite EACS guidance that all people living with HIV should be screened for HCV antibodies (annually in the case of MSM) and that HCV RNA testing should be carried out in cases of unexplained liver enzyme elevation.(28)

Barrier to hepatitis C treatment (34, 35)	
Patient barriers	**Provider barriers**
• Lack of knowledge • Concern regarding treatment side effects and efficacy of treatment • Socially and economically marginalised populations • Stigma	• Lack of treatment guidelines • Lack of awareness of impact of HIV on progression of HCV liver disease • Poor collaboration between infectious disease and hepatology specialists • Perception that coinfected patients are at high risk of non-adherence and re-infection • Concern regarding treatment efficacy and tolerability • Concerns about complexity of drug-drug interactions • Cost of treatment

In the absence of diagnosis and treatment, the risk of progression of liver disease in people living with HIV and HCV co-infection is higher than in the general population. The proportion of people with co-infection treated for hepatitis C remains very low (<5% per annum in the Eurosida cohort).(23) Although fully suppressive antiretroviral treatment reduces the risk of fibrosis progression in people with HIV and HCV co-infection, patients with F4 fibrosis remain at high risk of decompensation, especially where the platelet count is low (<105).(29-31) Averting decompensation and liver transplant is of particular importance in people with co-infection, whose post-transplant outcomes are unfavourable in comparison to monoinfected patients.(32) People with co-infection should be considered a high priority group for treatment with direct-acting antivirals (DAAs), as recommended in the American Association for the Study of Liver Diseases (AASLD) 2014 guidelines.(33)

Treatment with new interferon-free DAA regimens has resulted in cure rates above 80% in clinical trials in people with co-infections, including in people with liver cirrhosis and previous null responders with genotype 1a infection.(36-39) Some interferon-free DAA combinations have minimal drug-drug interactions with antiretroviral drugs. EACS guidelines recommend treatment for people with co-infection who have F2-F4 fibrosis with 2 or 3 DAAs, or pegylated interferon/ribavirin and 1 DAA (not telaprevir or boceprevir). Patients with compensated cirrhosis should be treated in specialist centres.(28) Cost represents the most substantial barrier to hepatitis C treatment in all European countries. Modelling of the cost burden for France showed that treatment of 56,000 patients with F2-F4 fibrosis with sofosbuvir and daclatasvir (+/- ribavirin) would cost 2.3–3.1 billion euros over three years.(40)

European activists have called for an EU-wide strategic action plan to address HCV diagnosis and treatment, and a drug pricing model that will permit universal access to treatment within current budget constraints. Activists have also called for unrestricted compassionate access to DAAs until pricing negotiations are completed, and for national screening and treatment guidelines which focus on clinical needs without regard to cost of treatment.(41)

WHO is developing a global health sector strategy on viral hepatitis and will conduct European consultations during Q1 2015. Consensus discussion identified the following priority measures for action on HCV coinfection:

- Substandard treatment is unacceptable.
- There is a need for support from clinical societies on advocacy against unacceptably high drug prices.
- TRIPS flexibilities are available to enable countries to pursue compulsory licenses on public health grounds.
- Guidelines should be updated more frequently to take into account the rapid pace of drug development and improvements in the standard of care.
- There are many lessons to be learnt from HIV for a successful viral hepatitis response in Europe.
- More research is urgently needed to characterise which patients are at highest risk of decompensation.
- More data are needed on the non-hepatic complications of hepatitis C in coinfected patients.

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Summary report: High-level Ministerial Meeting on HIV

28-29 November 2014, Rome, Italy

Introduction

The High-Level Ministerial Meeting on HIV was an initiative of the Italian Presidency of the European Union, which ended on 31 December 2014, designed to renew European Union commitment to combatting HIV and AIDS in the European region 10 years after the Dublin Declaration on HIV. The meeting convened EU institutions, Ministries of Health and major stakeholders including WHO Europe, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the European AIDS Clinical Society, and civil society representatives, including the Civil Society Forum on HIV/AIDS and European AIDS Treatment Group, for discussion on priorities and key concerns.

Vytenis Andriukaitis, European Commissioner for Health and Food Safety, opened the meeting with a strong statement of commitment to anti-discrimination, social inclusion and action against HIV in key affected populations.

The Commissioner noted the existence of major differences and the need for a European Union of health to overcome health inequalities in the EU, for cooperation with neighbouring countries and the need to address co-infections.

10 years of the HIV epidemic in Europe: ECDC-WHO reporting

Nedret Emiroglu, WHO Europe, Copenhagen, Denmark; Marc Sprenger, European Center for Disease Control, Stockholm, Sweden.

The Dublin Declaration (2004) stated an ambition of halting and reversing the increase in HIV diagnoses in the European region. Yet, across the European region as a whole, HIV diagnoses rose by 80% between 2004 and 2013. This increase is largely attributable to a substantial increase in new HIV diagnoses in Eastern Europe. Since 2004, the rate of new HIV diagnoses per 100,000 inhabitants has remained stable in Western and Central Europe (6.5 per 100,000 in 2004, 6.2 per 100,000 in 2013). In Eastern Europe, the rate of new HIV diagnoses has risen by 126% since 2004, to approximately 28 per 100,000 in 2013. Throughout the European region, 136,000 people were diagnosed with HIV in 2013, of which 29,157 were diagnosed in the European Union and EEA. In 2013, 59% of all HIV diagnoses in the European region occurred in the Russian Federation, 13% in Ukraine and 20% in Western and Central Europe.

HIV diagnoses, 2013, exposure categories (EU/EEA)		Change over previous decade
MSM	42%	+33%
Heterosexual	21%	-14%
Heterosexual (from country with generalised HIV epidemic)	11%	-61%
Injecting drug use	5%	-36%
Mother to child transmission	<1%	-37%
Unknown exposure route	20%	n/a

There is a sustained increase in the MSM epidemic in most countries. In the European Union, men who have sex with men are the most important group for HIV prevention activity and the increase of new cases in Central Europe is notable. Although new HIV diagnoses have declined in migrants from countries with generalised epidemics, analysis of the reason for the decline is lacking and information is lacking on HIV among recent migrants from Latin America and Asia and on HIV transmission within migrant communities. HIV diagnoses have decreased substantially in people who inject drugs but there have been outbreaks in some countries.

In comparison, HIV diagnoses have risen among people who inject drugs (+49%), heterosexuals (+195%) and 'other / undetermined' (+160%) in Eastern Europe since 2004. Of those with a known route of exposure, 50% were heterosexual and 45% were people who inject drugs. Better quality data on HIV among MSM in Eastern Europe are needed.

AIDS-related deaths in the EU/EEA have declined by 75% since 2004, to approximately 1000 per year, while the number of people receiving antiretroviral treatment has almost doubled, from 174,273 in 2004 to 333,699 in 2013.

The **cost of antiretroviral treatment** continues to prove a challenge for some countries in the region owing to budgetary pressures, a rise in HIV diagnoses and the cost of antiretroviral agents. Average costs vary substantially even between countries with similar incomes; whereas the annual average cost of antiretroviral therapy is 10,000 euros in The Netherlands, it is 17,500 euros in Germany. In Central and Southern Europe, the annual cost ranges from 7142 euros in Spain to 10,000 euros in Poland. In the Baltic states the annual cost is 3834 euros in Estonia but 7240 euros in Lithuania. Many countries in South East and Eastern Europe, which have been dependent on the Global Fund to buy drugs will face huge challenges once the Fund no longer supports them.

Countries in the European region report large variations in the **coverage of key HIV prevention and diagnostic measures**. Harm reduction coverage for people who inject drugs is monitored through the percentage of estimated drug users receiving opioid substitution therapy (OST) and the number of syringes distributed per person injecting drugs. Very low levels of OST (<5% coverage) were reported in Ukraine, Latvia, Moldova, Azerbaijan and Kazakhstan. Coverage above 60% was reported for only six countries: Denmark, Finland, Luxembourg, Malta, The Netherlands and Spain. Syringe distribution was low in most countries. Only five countries achieved coverage above 200 syringes per drug user per year (Croatia, Estonia, Kazakhstan, Norway and Spain) (12 EU states did not report data).

Uptake of **HIV testing** (measured by the proportion of the estimated population tested in 2013) was consistently low in key populations. Only six EU countries reported testing coverage greater than 50% among MSM in 2013, and only four reported testing coverage greater than 50% among people who inject drugs (15 EU countries did not report data).

Late diagnosis remains a critical problem throughout the region. In Eastern Europe and Central Asia, 49% of people are diagnosed with a CD4 cell count below 350 cells/mm^3. Late diagnosis is also a critical issue for migrant populations with poor access to health care.

Undocumented migrants are at particular disadvantage in relation to testing, prevention, treatment and care. They do not have access to antiretroviral treatment in 12 EU states, predominantly in Central Europe. In practice, undocumented migrants face practical barriers to access to testing and treatment in the majority of countries.

The European Center for Disease Control (ECDC) has identified five priorities for action in the European region to reverse the increase in HIV diagnoses.

1. **Targeted prevention at an appropriate scale for key populations** – men who have sex with men, people who inject drugs, migrants, prisoners and sex workers. There is variable coverage of harm reduction interventions even within the European Union.

2. **Greater coverage and frequency of HIV testing** in order to reduce late diagnosis. Testing should be community-based and governments should look for innovative methods of expanding the uptake of testing, as well as targeting key populations rather than the general population. At present, uptake of HIV testing is consistently low across all key populations.

3. **Scale up antiretroviral treatment coverage in Eastern Europe and make antiretroviral treatment and care accessible to undocumented migrants throughout the European Union**. National programmes need to improve rates of diagnosis and viral suppression in order to achieve the full impact of treatment as prevention. At present rates of diagnosis are still low, even in the best-performing countries.

4. **Scale up financing**, especially for civil society delivery of key prevention and harm reduction services.

5. **Strong political leadership**, both at national and European level, in order to mobilise funding and change attitudes towards HIV.

Key discussion points

- Early initiation of antiretroviral treatment has an important role to play in reducing HIV transmission. Maximising its potential requires political leadership in order to expand coverage in Eastern Europe.
- There is a need for better-quality data on the size of key populations in the European Union and Eastern Europe, and for enhanced surveillance capacity in order to characterise the burden of HIV in key populations and the local trajectories of the HIV epidemic.
- Greater involvement by lesbian, gay, bisexual and trans (LGBT) rights organisations in HIV prevention is needed in order to mobilise political attention to the HIV crisis among MSM in both Western and Eastern Europe.

How to ensure that no one is left behind

Licia Brussa, *International Committee on the Rights of Sex Workers in Europe; Ton Coenen, AIDS Fonds; Simone Marcotullio, NADIR, Italy; Pedro Marques, SER+ Associação Portuguesa para a Prevenção e Desafio à Sida, Portugal*

Highly effective and cost-effective interventions are not being put in place in Europe for economic and ideological reasons across interlocking fields of health.

The cost of inaction will be a rise in health care spending and a long-term loss of economic potential due to lost life-years of productivity among the predominantly young populations affected by HIV. Epidemics in the European region are concentrated and focused on key populations which face discrimination and barriers to care.

There is a need for ambitious resource targets and a major strategic investment in Eastern European public health by the European Union. In order to achieve these investments we need to reinvigorate activism and develop a new generation of activists to carry forward and expand civil society's achievements in the field of HIV over the past 30 years. In particular we need to engage the LGBT activist movement in this cause in order to achieve a change in political commitment.

People who inject drugs

A strong political commitment is needed to maintain and expand harm reduction programmes in order to sustain the observed reduction in HIV transmission and HIV prevalence among people who inject drugs in Western Europe, and to maintain low HIV prevalence among people who inject drugs in Central Europe. More investment is needed in harm reduction for migrant populations in the European region; evidence from Greece shows that the epidemic in people who inject drugs can expand quickly when harm reduction measures cease to be adequate or fail to reach new migrant populations. High levels of incarceration of drug users and a lack of harm reduction in prisons contribute to high HIV prevalence among people who inject drugs.

Sex workers

A range of policies and laws in the European region prevent sex workers from obtaining access to appropriate HIV prevention and sexual health services. Laws also prevent sex workers from controlling their work situations and force them to work in clandestine and unsafe spaces. Good practice in HIV prevention for sex work, and the space for public health interventions to enhance the sexual health of sex workers, is being eroded by an increasing focus on trafficking, exploitation of women and gender equity among policy makers. Coverage of the minimum package of HIV prevention for sex workers is very low in Eastern Europe. Only 3% of sex workers in Russia and Ukraine have access to the minimum HIV prevention package.

Men who have sex with men

HIV prevalence is continuing to rise among MSM in Western and Central Europe due to low levels of investment in HIV prevention for gay men, and to syndemic factors. These include high levels of drug and alcohol use, depression and negative societal attitudes towards homosexuality. A historic lack of HIV prevention and sexual health promotion that focuses on MSM living with HIV also contributes to ongoing transmission and to high levels of sexually transmitted infections among MSM living with HIV.

The treatment cascade in Europe

Martin Donoghoe, WHO Europe; Enrico Girardi, National Institute for Infectious Diseases L. Spallanzani, Italy; Nikos Dedes, European AIDS Treatment Group

One third of people living with HIV in the European region do not know their HIV status and are unable to benefit from antiretroviral therapy. Approximately 50% are late presenters (diagnosed at a CD4 count below 350 cells/mm^3). AIDS diagnoses have increased threefold in Eastern Europe since 2004, whereas AIDS diagnoses have declined by 60% during the same period in Western and Central Europe. Improving rates of HIV diagnosis, linkage to care, treatment initiation and retention in care are essential for the reduction of AIDS-related morbidity and mortality in the region.

Antiretroviral coverage of eligible persons (CD4 < 350) remains extremely low in Eastern Europe; only 35% of people eligible for treatment were receiving antiretroviral therapy in 2012, one of the lowest proportions in the world. The low coverage of treatment also has consequences for prevention.

Comparative treatment cascades in Europe and Central Asia

	Estimated HIV	Diagnosed	Linked to care	Retained in care	On ART	Virally suppressed
France	149,000	81%	n/a	74%	16%	52%
Armenia	3700	44%	n/a	28%	16%	14%
Azerbaijan	9200	47%	n/a	28%	14%	10%
Belarus	24000	50%	n/a	41%	18%	13%
Georgia	4900	52%	44%	38%	26%	20%
Kyrgyzstan	7600	67%	n/a	28%	12%	?
Russia	1,360,000	49%	38%	35%	11.5%	9% (<1000)
Ukraine	237,000	86%	59%	?	?	17%

Improving rates of HIV diagnosis is the first step towards reducing late presentation, AIDS diagnoses and deaths in the European region.

Improving the coverage of antiretroviral treatment (ART) is also essential. It is important for policy makers and governments to understand the public health and economic benefits of ART. ART is one of the few medical interventions that is not only cost-effective but cost saving. Even when considered strictly in terms of health system costs, ART averts hospitalisation costs. When considered in terms of its impact on life expectancy, ART preserves a cohort of younger adults who can be economically productive for a normal lifespan if treated optimally. When considered in terms of its preventive benefit, ART has the potential to avert subsequent infections over the lifetime of the individual, thus averting future treatment costs. This 'multiplier effect' is not captured in most cost-effectiveness analyses and urgently requires consideration in countries where HIV prevalence continues to rise. There is also a need for advocates to develop a more robust set of cost estimates demonstrating the cost-saving potential of ART for countries where coverage is sub-optimal.

Access to innovative medicines

John Ryan, European Commission, Directorate General for Health and Consumer Safety, Luis Mendão, GAT and EATG

Equitable access to innovative medicines for treatment of hepatitis C was raised by the French government at the European Union Council of Health Ministers in 2014 and is now the subject of discussions in a Council Working Party and the network of competent authorities. The European Commission does not have a legal competence to regulate the prices of medicines; this is a member-state responsibility. There are several EU instruments which may be used to improve access:

- The Commission can improve the exchange of information regarding prices paid for medicines in member states in order to improve transparency, which will aid individual member states to achieve better prices and more consistent and predictable pricing.
- The new Joint Procurement Mechanism, established by the Cross Border Decision on Serious Health Threats, can be used to achieve economies of scale in purchasing. The Cross Border Decision specifically mentions hepatitis C. Four states can launch a procedure and involvement in a procedure is voluntary and open to all states that have signed up to use of the mechanism. 18 states have already signed, 2 were due to sign in December 2014, and 5 more states will sign in 2015.

Establishment of a European Union mechanism for health technology assessment has been proposed. At present European states conduct 28 separate assessments on the same products. The European Commission is pushing strongly for further joint actions on Health Technology Assessment.

The price of direct-acting antivirals for hepatitis C poses a significant challenge for health systems in the European region. Despite being cost-effective and of lower lifetime cost than antiretroviral treatment, the cost of DAA treatment is unaffordable even for health systems in the wealthiest EU states, due to the large numbers of persons in need of treatment. The pricing of DAAs and other innovative medicines threatens to jeopardise the future of European health systems. If health systems cannot pay escalating drug costs, the future profitability of the pharmaceutical industry in Europe is threatened, and the future existence of a research-based pharmaceutical industry in the region is called into question. The current pricing model is unsustainable and industry needs to work with payers and patient groups to develop a 'win-win' pricing model that will permit access and innovation.

Financing the HIV response in the European region

Christoph Benn, Global Fund

The Global Fund to Fight AIDS, Tuberculosis and Malaria has given US $1.4 billion to the Eastern Europe & Central Asia (EECA) region since 2004, supporting antiretroviral treatment for a cumulative 85,000 people since 2004. A further $680 million is committed to the region for the period 2014-16 (28% to Ukraine, 10% to Uzbekistan and 9% to Georgia) with the aim of stabilising HIV prevalence and containing the spread of multidrug-resistant and extensively drug resistant TB. Maintaining political support for funding of HIV and TB programming in the EECA region is challenging due to the strength of political commitment to poverty-focused funding allocations, especially among Northern European foreign and development ministries. In order to build political support for an enhanced programmatic response in EECA, greater advocacy is needed at national level as well as at multilateral level.

Discussion points:

- There was general agreement that Germany, the United Kingdom and the Nordic countries need to be lobbied to change their funding policies towards EECA.
- Multisectoral responses are integral to successful HIV responses in sub-Saharan Africa and we need to move towards a similar model in order to address HIV and TB in Eastern Europe, involving Ministries of Justice and Ministries of the Interior.

Key conference conclusions

The conference participants agreed that renewed political commitment at European level is needed and that draft text of a declaration on HIV and AIDS put forward by the Italian Presidency needs further discussion. The Italian Presidency committed to bring the conclusions of the High Level meeting for further discussion among EU member states, in order to agree on a set of updated targets building on the Dublin Declaration. The declaration will be followed up with the Latvian and Luxembourg Presidency and the Commission offered to support the process. It was also suggested to invite the upcoming Presidencies and other interested member states to join the External Advisory Board.

The need for European action

1. **HIV and co-morbidities**, notably tuberculosis, viral hepatitis, and other sexually transmitted infections **continue to represent a serious challenge to public health, human rights, and equity in Europe.** Contrary to the global decreasing trend, new HIV infections are rising, especially in Eastern Europe and Central Asia, and across the region among key affected populations left behind: people who inject drugs and their sexual partners, men who have sex with men, transgender people, migrants and ethnic minorities, sex workers and prisoners.

2. **Ambitious goals and actions are needed:** By 2020, Europe should ensure coverage of comprehensive, integrated and people-centered packages for prevention, diagnosis, treatment and care of HIV and co-morbidities for each key population and address specific needs for subgroups, in accordance with WHO guidelines.

3. **Europe today has the knowledge and resources to reach the goal of ending the AIDS epidemic.** Active political leadership and vigilance at national and European levels are needed to ensure that evidence-based policies are implemented, that focus and resources are sustained, targeted and at the scale of what is needed.

Key populations

1. In EU/EEA, many countries have successfully curbed the HIV epidemic among drug users through the implementation of targeted and comprehensive harm reduction measures. Continued attention and determination is needed to **avert an erosion of our investments in harm reduction and the progress already made** is essential to end HIV in people who inject drugs.

2. Scaling up support for an effective response to the escalating HIV epidemic among people who inject drugs and their sexual partners particularly in Eastern Europe and Central Asia, and to **ensure the full implementation of comprehensive harm reduction programmes** (including opioid substitution therapy) **for people who inject drugs, including in prisons across Europe.**

3. Europe has concentrated epidemics, which require **political leadership to overcome stigma and discrimination** experienced by people living with HIV and key populations, and AIDS-related deaths **and the scaling up of resources** to meet the needs of key affected population and public health.

4. **Innovative approaches** are urgently required to address the epidemics of HIV, HCV and other sexually transmitted infections among men who have sex with men, and the disproportionally high and increasing number of new infections among migrant populations in some countries.

5. Governments and other actors must ensure that **people living with HIV and key populations are at the centre of the HIV and co-infection response.** There is urgent need to invest in their capacity to become meaningfully involved at all stages of research, planning, implementation and evaluation.

Access to treatment

1. **Universal access to health services must be ensured for all,** regardless of residency or insurance status of the person.

2. **The high cost of treatment**, medicines and diagnostics for HIV and co-morbidities represents **a significant barrier** for harnessing the full benefits of HIV treatment as a unique tool to prevent HIV-related illness and disability, avert AIDS-related deaths and prevent new HIV infections.

3. **Governments and the EU should find ways to achieve equitable and affordable access to effective medicines and diagnostics for HIV and co-morbidities**, including tuberculosis and viral hepatitis, to ensure sustainable national healthcare systems. This could be done through cooperation on strategies to effectively manage pharmaceutical expenditure, including on issues related to affordable pricing, use of generic medicines, compulsory licensing, medical devices, and small markets.