

Late presentation in HIV-infected injecting drug users - a huge challenge for the Romanian health-care system

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Abstract: *Background.* HIV-infected injecting drug users (HIV-IDUs) are a major challenge to the Romanian healthcare system due to their high morbidity, mortality and health-care costs.

Objective. The aim of this study was to determine the prevalence of late presenters (LP) among HIV-IDUs admitted to “Victor Babes” Clinical Hospital for Infectious Diseases, Bucharest and to evaluate their demographic and clinical characteristics.

Methods. We performed a prospective study on HIV-IDUs diagnosed with severe immunosuppression, admitted between January 2009 and December 2014. HIV-IDUs with CD4 cell counts $< 350/\text{mm}^3$ were considered LP and those with CD4 to a tertiary facility $< 200/\text{mm}^3$ were defined with advanced HIV disease (AHD). These two groups were compared to a group of the HIV-IDUs that was diagnosed early in the evolution of illness (CD4 cell count $> 350/\text{mm}^3$). Statistical analysis was performed using SPSS v 20.0.

Results. Out of 495 HIV-IDUs admitted during the study period, 238 (48.0%) were LP and 168 (33.7%) had AHD. The proportion of LP increased from 37.5% in 2009 to 52.6% in 2014 ($0 < 0.001$). Almost all HIV-IDUs, regardless of CD4 cell count, were young males (413, 83.4%), from urban areas (453, 91.5%), unemployed (393, 79.3%) and with low educational level (381, 76.9%). The median age at drug use initiation of 19 years (IQR 16-24) and the median duration of drug use at 9 years (IQR 4-13), were similar in both groups. More than half of all HIV-IDUs initially used intravenous heroin and afterwards legal highs (339, 68.4%) and (81, 16.3%) used only legal highs. The median CD4 cell count for the LPs was $104 \text{ cells}/\text{mm}^3$ (IQR 24-220) and the median HIV viral load $5.44 \log_{10} \text{ copies}/\text{mL}$ (IQR 5.00-6.00). Compared to early diagnosed HIV-IDUs (257), late presenters were more frequently diagnosed with opportunistic infections, especially tuberculosis (117, 49.1%) vs. (37, 14.3%), $p < 0.0001$ and severe bacterial infections, mainly respiratory (54, 22.6%) vs. (46, 17.8%) $p = 0.02$. Mortality was higher in LPs versus early presenters IDU (7, 2.7%) vs. (54, 22.6%) respectively $p < 0.0001$.

Conclusions. The proportion of LPs among HIV-IDUs diagnosed in our hospital increased alarmingly over the last few years. There were no significant differences regarding socio-demographic characteristics and drug use behaviour between late presenters and those diagnosed early, but LPs were more often diagnosed with opportunistic infections and had a significantly higher mortality rate.

Key Words: HIV, IDUs, late presentation.

Human Immunodeficiency Virus (HIV) infection represents a major global public health problem. Data published by the European Center for Disease control (ECDC) at the end of 2015 showed that 142, 197 new HIV cases were diagnosed during the previous year in the WHO European Region [1].

Despite significant efforts made in HIV prevention and control, the overall rate of HIV diagnosis is still high, and 48% of new HIV-infected patients were diagnosed as late presenters (LP)(CD4 cell count $< 350/\text{mm}^3$) with 27% having advanced HIV disease (AHD) (CD4 cell count $< 200/\text{mm}^3$) [1-3]. Also, it is estimated that a high

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proportion of people are still unaware of their HIV status and that the number of LP will increase.

Late presentation is often associated with a more rapid clinical evolution, higher mortality rates, poor response to treatment, more frequent toxicity secondary to antiretroviral medication, increased healthcare costs and higher rates of HIV transmission [3-5].

According to the national reports from Romania, by the end of 2015, 13, 766 people were living with HIV [6], more than 6000 of them belonging to the homogeneous cohort of children infected with clade F1 by parenteral mode in the late 80s [7-9]. However, in the last years, an alarming increase in the number of newly HIV-infected cases among injecting drug users (IDUs) has been reported, similar to the general European trend [7]. The increase in the number of IDUs diagnosed with HIV was consecutive with the spread of use of new psychoactive drugs, known as “ethnobotanicals”. Most of the previous heroin users in Romania switched to the new legal highs because of easier access, and lower price. These new drugs, available on the market as “bath salts” or “plant food”, include mephedrone or methylone and a combination of different other chemicals. They are cathinone derivatives with amphetamine-like effects, inducing euphoria and violent behaviour, associated with cardiac arrhythmias and increased risk of death. Also, they are highly addictive and require multiple administrations per day. Therefore the risk of acquiring HIV and infections with hepatitis C, B and D is very high [10-12].

In 2009, the beginning of the drug epidemics in Romania, the majority of HIV-IDUs were “real time” presenters to the hospital, diagnosed early during infection. Nevertheless, as the incidence of HIV among IDUs increased from 3% in 2010 to 22% in 2015, with a peak of 29.23% in 2013 [6], the incidence of late presentation in this subgroup of patients is rising.

OBJECTIVE

The aim of our study was to determine the prevalence of LP among HIV-IDUs admitted to a single tertiary facility and to evaluate their demographic and clinical characteristics.

METHODS

We performed a prospective study on HIV-infected IDUs (HIV-IDUs) that were diagnosed with severe immunosuppression and were admitted to “Victor Babes” Clinical Hospital for Infectious and Tropical Diseases, Bucharest, between January 2009 and December 2014. Those with CD4 cell counts < 350/mm³ were considered LP and those with CD4 <200/mm³ were defined as having AHD.

Socio-demographic characteristics (age, sex,

level of education, occupation, urban/rural areas), as well as those related to drug use behaviour (age at drug use initiation, time on drug use, type of narcotics) and clinical outcomes were obtained from questionnaires and hospital medical records.

We compared the characteristics of LPs with a group of early diagnosed HIV-IDUs (EP-IDUs), having a CD4 cell count above 350/mm³ (EP- IDUs).

CD4 cell counts were determined by four colour flow cytometry using the BD MultiTest™ CD3/CD8/CD45/CD4 (Becton Dickinson, San Jose, CA, USA) in the dual platform with haematology analyser. HIV viral load was determined with a commercial nucleic acid amplification test (COBAS AmpliPrep/ COBAS TaqMan HIV-1 Test Version 2.0, Roche Molecular Systems, Branchburg, NJ, USA), with a lower detection limit of 20 copies of HIV RNA/mL and a linear range between 20 and 10000000 copies HIV RNA/mL.

HIV viral load was available only for 100 HIV-IDUs with late presentation.

Statistical analysis

Statistical analysis was performed using SPSS v 20.0. The two study groups were compared using unpaired t test or Mann-Whitney test for continuous variables (group means) and Fischer's exact or chi-square test for nominal variables, to determine the association between socio-demographic characteristics, opportunistic/severe bacterial infections or evolution and CD4 cell count. A p-value below 0.05 was considered to be statistically significant.

RESULTS

Out of 495 HIV-infected IDUs admitted in our hospital between 2009 and 2014, 238 (48.0%) were diagnosed as LP and 168 (33.7%) with AHD.

The number of HIV-IDUs with severe immunosuppression increased significantly between 2009 (37.5%) and 2014 (52.6%, p<0.001) with a peak in 2013. In the last three years, half of the IDUs with HIV were diagnosed as LPs: 47.8% in 2012, 51.6% in 2013

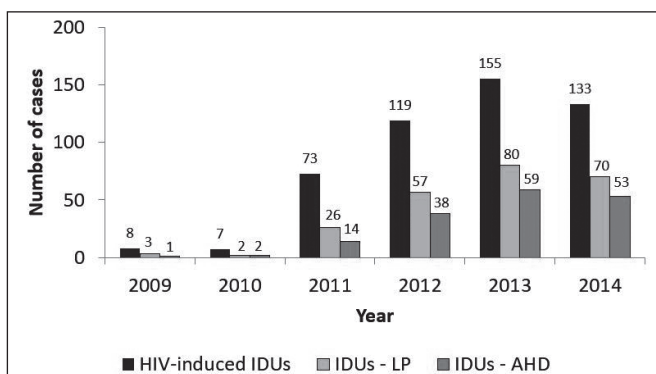


Figure 1. Number of HIV-infected IDUs diagnosed as LP and with AHD admitted to “Victor Babes” Clinical Hospital, Bucharest.

and 52.6% in 2014. More than a third of them had AHD (31.9% in 2012, 38% in 2013 and 39.8% in 2014) (Fig. 1).

Most HIV-IDUs, regardless of CD4 cell count, were young men (413, 83.4%), from urban areas (453, 91.5%), unemployed (393, 79.3%) and with a low level of education (381, 76.9%). The median age at HIV diagnosis was 29.5 years [IQR 25-34]; almost 20% of them had a history of incarceration (Table 1).

There was no difference regarding the age when they started the drug abuse between LP IDUs and early diagnosed IDUs (p=0.97). However, we noticed a statistically significant difference concerning the time of mean duration of drug abuse use between early diagnosed IDUs and those diagnosed as LPs: 8 years [IQR 4-13] vs. 10 years [IQR 5-14], p=0.04, respectively.

Heroin was used by 75 (15.1%) IDUs, while 81 (16.3%) IDUs injected only legal highs. More than half of all IDUs, 339 (68.4%) reported injecting both heroin and psychoactive drugs (Table 2).

The concomitant use of other drugs (LSD, weed, cocaine) was more frequent in early presenter IDUs compared to LP IDUs (24, 9.3% vs. 10, 4.2%, p=0.03) or AHD (24, 9.3% vs. 5, 2.9%, p=0.01).

The median CD4 cell count at HIV diagnosis was 104/mm³ [IQR 24-220] in LPs, with a significant decrease over the study period from 160/mm³ in 2009 to 56/mm³ in 2014 (p<0.001). The median CD4 cell count at HIV diagnosis for patients diagnosed with AHD was 42 cells/mm³ [IQR 15-111].

The median HIV viral load (log₁₀ copies/mL) was lower in EP- IDUs compared to LPs 4.93 [IQR 4.26 - 5.47] vs. 5.44 [IQR 5.00 - 6.00], p=0.005.

LP IDUs were more frequently diagnosed with opportunistic infections and with AIDS-related malignancies (Table 3). The most frequent diagnosed opportunistic infections were: tuberculosis (117/238, 49.1%), cerebral toxoplasmosis (3), Pneumocystis jirovecii pneumonia (1) and cerebral cryptococcosis (1). Fifteen patients were diagnosed with multidrug-resistant (MDR) TB, most of them being LPs (13) vs. 2 EP-IDUs. There were nine patients with extensive drug resistance (TB XDR), almost all of them being LPs (8/13) vs. 1/2 in EP-IDUs.

LP IDUs were diagnosed more frequently with severe pulmonary infections (22.6%), while EP-IDUs had predominant skin and soft tissues infections

Table 1. Socio-demographic characteristics in HIV-infected IDUs: comparison between early diagnosed IDUs and IDUs-LP

Socio-demographic characteristics	Total n=495	EP-IDUs n=257	LP- IDUs n=238	P value
Male sex n (%)	413 (83.4)	211 (82.1)	202 (84.8)	0.40
Urban areas n (%)	453 (91.5)	236 (91.8)	217 (91.1)	0.79
Unemployed n (%)	393 (79.3)	200 (77.8)	193 (81.0)	0.36
Low level of education n (%)	381 (76.9)	193 (75.0)	188 (78.9)	0.79
Median age at HIV diagnosis years (IQR)	29.5 (25-34)	29 (25- 33)	30 (25 – 34)	0.09
Imprisonment n (%)	102 (20.6)	57 (22.1)	45 (18.9)	0.36

Table 2. Drug use behaviour in HIV-infected IDUs: comparison between EP - IDUs and LP - IDUs

Drug use behaviour	Total n=495	EP-IDUs n=257	LP IDUs n=238	P value
Median age at drug use initiation years (IQR)	19 (16 – 24)	19 (16 – 24)	19 (16 – 24)	0.97
Median duration of time on drug use years (IQR)	9 (4 – 13)	8 (4 – 13)	10 (5 – 14)	0.04
Heroin& legal highs n (%)	339 (68.4)	179 (69.5)	160 (67.2)	0.56
Heroin n (%)	75 (15.1)	42 (16.3)	33 (13.8)	0.44
Legal highs n (%)	81 (16.3)	36 (14.0)	45 (18.9)	0.14

Table 3. Clinical manifestations and mortality rate: comparison between EP - IDUs and LP- IDUs

	Total n=495	EP-IDUs n=257	LP- IDUs n=238	P value
Tuberculosis n (%)	154 (31.1)	37 (14.3)	117 (49.1)	<0.0001
Other opportunistic infections n (%)	7 (1.4)	2 (0.7)	5 (2.1)	0.21
AIDS-related malignancies n (%)	6 (1.2)	1 (0.3)	5 (2.1)	0.08
Pulmonary infections n (%)	100 (20.2)	46 (17.8)	54 (22.6)	0.18
Sepsis n (%)	38 (7.6)	18 (7.0)	20 (8.4)	0.61
Right-sided endocarditis n (%)	32 (6.4)	14 (5.4)	18 (7.5)	0.36
Skin infections n (%)	50 (10.1)	30 (11.6)	20 (8.4)	0.22
Other infections n (%)	40 (8.0)	14 (5.4)	26 (10.9)	0.03
Mortality rate n (%)	61 (12.3)	7 (2.7)	54 (22.6)	0.02

EP- IDUs: early presenter IDUs, LP- IDUs: late presenter IDUs.

11.6%. The proportion of sepsis (8.4%) and right-sided endocarditis (7.5%) was higher for LPs, but it did not reach statistical significance. *Staphylococcus aureus* was most often detected in patients diagnosed with sepsis and endocarditis, but with no statistical difference between the two groups (25/38, 65.7% in LP IDUs vs. 24/32, 75% in EP-IDUs, $p=0.40$). The mortality rate among patients diagnosed with right-sided endocarditis was higher for LPs compared to EP - IDUs (7/18, 38.8% vs. 2/14, 14.2%, $p=0.12$).

The overall mortality rate was 12.3% (61), significantly higher for LP IDUs compared to EP- IDUs: 2.7% (7/257) vs. 22.6% (54/238), $p<0.0001$.

DISCUSSIONS

In this study, we reported a high prevalence of late presenters among HIV-infected IDUs, including an increased number of patients diagnosed with AHD. The proportion of late presentation has increased every year, more than 50% in the last two years. These results are concordant with the recent data at the national level, indicating that more than half of Romanian IDUs diagnosed with HIV in 2014 were LPs [13], as well as with data from other similar Southern and Eastern European countries indicating high percentage of LP [3, 4, 14, 15] among IDUs. The ECDC reported that the proportion of LPs diagnosed in the last years (61%), was one of the highest in EU and EEA [1].

These increased percentages, associated with an ascendant trend of LP among IDU are in contrast with the old idea of IDUs being “early presenters” to the hospital. Historically, in Romania patients infected with HIV by heterosexual contact were more commonly late-presenters, while MSMs and IDUs were diagnosed relatively early during infection [13, 16].

Insufficient public health interventions associated with delayed testing, counselling or linkage to harm reduction programs are considered to be responsible for the recent HIV outbreaks among IDUs and the increased number of LPs among these high-risk populations.

We found no difference regarding socio-demographic characteristics or drug use behaviour between LP IDUs and EP - IDUs, their profile being similar to those described in studies performed across Europe [17, 18-20]. However, we did find that a longer period of drug use was associated with severe immunosuppression at HIV diagnosis.

Most IDUs from our study reported being former heroin users, who tried to quit heroin by switching to psychoactive drugs while these were legal, and ended up with a more severe addiction, both to heroin and the former legal highs. Since the end of 2008, when the new psychoactive drugs became very popular among young people, the drug market from Romania can be described as unbalanced, due to variations between a high level

of heroin use and the important increase in the use of psychoactive drugs in a short period of time [21]. It is possible that most of the IDUs were infected around the same period (2010-2011) when access to sterile syringe needles fell dramatically following the end of international grants (Global Fund, UNODC) that were funding both Harm Reduction programs and substitution treatment interventions. Only 49% of IDUs reported visiting exchange programs in 2010 vs. 76% in 2009 [22]. Similar situations have been described in Israel or Greece at the end of 2011 when, due to economic reasons, heroin addicts tended to adopt more high risk injecting behaviours [23]. As a consequence of the increased use of amphetamine-like stimulants, the number of newly diagnosed HIV-infected IDUs registered an alarming increase, especially among homeless young males from dramatic urban areas [11, 23].

According to outreach social workers some of the long-term survivors infected with HIV during childhood, and now aged between 25 and 28 years, are already prone to drug usage, a fact that amplifies the risk of HIV transmission. The possibility of the spread of HIV drug resistant variants is high because a proportion of these patients have been treated with multiple antiretroviral regimens, with cumulative toxicities and multiple treatment failures.

Tuberculosis (TB) was the most common opportunistic infection diagnosed in IDUs in our study. The ECDC also reported TB as being the most common AIDS-defining disease diagnosed in IDUs [1], while according to CNLAS (National Committee for Fight Against HIV/AIDS), 22% of Romanian HIV-infected IDUs were diagnosed with TB in 2014 [11]. Data from the literature highlights the fact that TB incidence is higher in IDUs and that recreational drug users have a higher risk to develop TB regardless of their HIV status [24-26]. It was also suggested that the duration of intravenous drug use is associated with a greater risk for TB. Compared to other HIV-infected patients, IDUs have a higher risk for TB due to their lifestyle and high-risk behaviours (needle sharing, alcohol abuse or history of imprisonment). The risk is even higher if they are diagnosed as LPs, as a consequence of severe immunosuppression [19, 26 – 30]. It is a known fact that CD4 cells depletion is one of the most important factors responsible for the susceptibility to primary TB infection or latent TB reactivation [31].

Due to their severe immunosuppression, LPs from our study were also more frequently diagnosed with severe bacterial infections, especially with pulmonary involvement, possibly due to respiratory damage caused by drugs and smoking [32]. Interestingly, skin and soft tissues infections, probably due to non-sterile injecting equipment, were diagnosed in our study more commonly in EP- IDUs. Data from literature reports high incidence and severity of these infections diagnosed most often in IDUs with severe immunosuppression [33-36]. Also,

according to studies from Israel, cathinone derivatives use was associated with a higher risk of acquiring the severe bacterial infection. Unlike heroin, legal highs use seems to be a more social activity that requires cold water for drug preparation, to avoid altering its quality. As a consequence of the lack of heating, associated with increased proportion of needle sharing, the infectious risks are higher [11]. As expected, due to this high frequency of opportunistic infections and severe bacterial infections, the mortality rate was significantly increased in IDUs diagnosed with late presentation.

However, this study signals the impact of late HIV diagnosis on both the clinical evolution of the patient and on the public health system, from a social and economic point of view.

LIMITATIONS

The fact that the study was conducted in a single centre limits the information and does not express the national prevalence of late presenting IDUs, since the majority of Romanian IDUs are concentrated in Bucharest

and surrounding areas and that a high percentage of them are diagnosed and treated in our hospital.

CONCLUSIONS

The proportion of LP among HIV-infected IDUs was high and with an ascending trend. LP IDUs were predominantly young males, unemployed, with a low level of education and with a high risk of developing TB and other bacterial infections. Management and long-term outcome of HIV-infected IDUs are poor due to their lack of adherence to cART, drug-drug interactions and toxicities, neuro-psychiatric disorders and the high risk of acquiring severe viral and bacterial infections. We consider that more efforts need to be done regarding HIV testing and prevention methods among people with high-risk behaviours from Romania, particularly IDUs, and to allow easy access to care and treatment of these vulnerable group.

Conflict of interest. The authors declare that they have no conflict of interest concerning this article.

References

1. European Centre for Disease Prevention and Control, WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2014. Stockholm: ECDC; 2015.
2. Likatavicius G, Van de Laar M. HIV and AIDS in the European Union, 2011. *Euro Surveill.* 2012;17(48). pii: 20329.
3. Camoni L, Raimondo M, Regine V, Salfa MC, Suligoi B; regional representatives of the HIV Surveillance System. *BMC Public Health.* 2013 Mar 27;13:281.
4. Celesia BM, Castronuovo D, Pinzone MR. Late presentation of HIV infection: predictors of delayed diagnosis and survival in Eastern Sicily; *European Review for Medical and Pharmacological Sciences;* 2013; 17: 2218-2224.
5. Buetikofer S, Wandeler G, Kouyos R, Weber R, Ledergerber B. Prevalence and risk factors of late presentation for HIV diagnosis and care in a tertiary referral centre in Switzerland; *Swiss Med Wkly.* 2014; 144:w13961.
6. Streinu-Cercel A, Mardarescu M, Benea EO, Petrea S. Evolutia infectiei HIV/SIDA in Romania, decembrie 2015, site-ul Comisiei Nationale de Lupta Anti-SIDA, http://www.cnlas.ro/images/doc/31122015_rom.pdf si http://www.cnlas.ro/images/doc/01122015_rom.pdf
7. Streinu-Cercel A, Mardarescu M, Benea EO, Petrea S. Evolutia infectiei HIV/SIDA in Romania, decembrie 2015, site-ul Comisiei Nationale de Lupta Anti-SIDA http://www.cnlas.ro/images/doc/spec_chall_HIV.pdf
8. Apetrei C, Necula A, Hol-Hansen C. HIV-1 diversity in Romania; *AIDS:* 1998; Volume 12; 1079-10859.
9. Guimaraes ML, Vicente AC, Otsuki K. Close phylogenetic relationships between Angolan and Romanian HIV-1 subtype F1 isoaltes; *Retrovirology;* 2009; 6:39.
10. Maftai L. The main characteristics of the Romanian illegal drug markets; *Eastern Journal of European Studies,* 2012, 3:189-204.
11. Katchman E, Savyon M, Chemtob D. An Outbreak of Primary HIV Infection among Injecting Drug Users in Tel Aviv, Israel Associated with Changes in the Illicit Drug Use Practices; 14th European AIDSConference, Brussels, abstract PS11/4, 2013.
12. EMCDDA - Synthetic cathinones drug profile, <http://www.emcdda.europa.eu/publications/drug-profiles/synthetic-cathinones#headersection>.
13. Streinu-Cercel A, Mardarescu M, Benea EO, Petrea S. Evolutia infectiei HIV/SIDA in Romania, decembrie 2015, site-ul Comisiei Nationale de Lupta Anti-SIDA http://www.cnlas.ro/images/doc/31122014_eng.pdf.
14. Sobrino-Vegas P, Perez-Hoyos S, Geskus R. Imputation of the Date of HIV Seroconversion in a Cohort of Seroprevalent Subjects: Implications for Analysis of Late HIV diagnosis; *AIDS Res Treat* 2012, 2012:725412.
15. Mocroft A, Lundgren JD, Sabin ML. Risk Factors and Outcomes for Late Presentation for HIV-Positive Persons in Europe: Results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE); *PLOS Medicine;* September 2013; volume 10; issue 9; e1001510.
16. Oprea CA, Erscoiu SM, Radoi R. Late presentation in newly diagnosed HIV infected patients in a Romanian regional center; *EACS Conference* 2013, PE 21/34.
17. Ndiaye B, Salleron J, Vincent A. Factors associated with presentation to care with advanced HIV disease in Brussels and Northern France: 1997-2007; 2011; *BMC Infect Dis* 11:11.
18. Rützel K, Karnite A, Talu A, Abel-Ollo K, Kirvelaite G, Kliiman K, Loit HM, Uusküla A. Prevalence of IGRA – positivity and risk factors for tuberculosis among injecting drug users in Estonia and Latvia. *Int J Drug Policy.* 2014;25(1):175-8.
19. Pimpin L, Drumright LN, Kruijshaar ME, Abubakar I, Rice B, Delpech V, Hollo V, Amato-Gauci A, Manissero D, Ködmön C. Tuberculosis and HIV co-infection in European Union and European Economic Area countries. *Eur Respir J.* 2011;38(6):1382-92.

20. Paraskevis D, Nikolopoulos G, Fotiou A, Tsiara C, Paraskeva D, Sypsa V, Lazanas M, Gargalianos P, Psychogiou M, Skoutelis A, Wiessing L, Friedman SR, Jarlais DC, Terzidou M, Kremastinou J, Malliori M, Hatzakis A. Economic recession and emergence of an HIV-1 outbreak among drug injectors in Athens metropolitan area: a longitudinal study. *PLoS One*. 2013;8(11):e78941.
21. Botescu A. Risk assessment of new psychoactive substances consumption among children and youth in Romania. ALPHA MDN Publishing House Bucharest 2012.
22. EMCDDA/ECDC; Joint EMCDDA and ECDC rapid risk assessment HIV in injecting drug users in the EU/EEA, following a reported increase of cases in Greece and Romania. 2012.
23. Fotiou A, Micha K, Paraskevis D. HIV outbreak among injecting drug users in Greece. An updated report for the EMCDDA on the recent outbreak of HIV infections among drug injectors in Greece. 31 October 2012
24. Batista Jd, de Albuquerque Mde F, Maruza M, Ximenes RA, Santos ML, Montarroyos UR, de Barros Miranda-Filho D, Lacerda HR, Rodrigues LC. Incidence and risk factors for tuberculosis in people living with HIV. Cohort from HIV Referral Health Centers in Recife, Brasil. *PLoS One*. 2013 May 10;8(5):e63916.
25. WHO Global Tuberculosis Control: Surveillance, Planning, Financing. In; World Health Organisation, (2008) editor Geneva.
26. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update. *Clin Infect Dis*; 2009;48: 72-82.
27. Lot F, Pinget R, Cazein F. Frequency and risk factors for tuberculosis as an AIDS-defining illness, in France; *Bull Epidemiol Hebdomadaire*; 2009; 113.
28. Martín V, Caylà JA, Bolea A, Castilla J. Mycobacterium tuberculosis and human immunodeficiency virus co-infection in intravenous drug users on admission to prison. *Int J Tuberc Lung Dis*; 2000; 4: 41-46.
29. Caminal Montero L, Trapiella Martínez L, Telenti Asensio M, Fernández Bernaldo De Quirós J. Characteristic of tuberculosis in a general hospital during the period 1993-1998; Analysis of resistance and HIV coinfection; *Enferm Infecc Microbiol Clin*; 2002; 20: 68-73.
30. Diez M, Diaz A, Bleda MJ, Aldamiz M, Camafort M, Camino X, Cepeda C, Costa A, Ferrero O, Gejjo P, Iribarren JA, Moreno S, Moreno ME, Labarga P, Pinilla J, Portu J, Pulido F, Rosa C, Santamaria JM, Telenti M, Trapiella L, Trastoy M, Viciano P. Prevalence of M. tuberculosis infection and tuberculosis disease among HIV-infected people in Spain; *Int J Tuberc Lung Dis*; 2007; 11: 1196-1202.
31. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. Tuberculosis and HIV Co-infection. *PLoS Pathog*. 2012;8(2):e1002464.
32. Schluger NW, El-Bassel N, Hermosilla S, Terlikbayeva A, Darisheva M, Aifah A, Galea S. Review Tuberculosis, drug use and HIV infection in Central Asia: An urgent need for attention. *Drug Alcohol Depend*. 2013;132 Suppl 1:S32-6.
33. Gyarmathy VA, Neaigus A, Ujhelyi E. Vulnerability to drug-related infections and co-infections among injecting drug users in Budapest, Hungary. *European Journal of Public Health*; 2009; Vol. 19, 260–265.
34. Bruce RD, Altice FL. Clinical care of the HIV-infected drug user. *Infect Dis Clin North Am*;2007 March; 21(1):149-79.
35. Yombi JC, Jonckheere S, Vincent A, Wilmes D, Vandercam B, Belkhir L. Late presentation for human immunodeficiency virus (HIV) diagnosis: results of a Belgian single centre. *Acta Clin Belg*. 2014;69(1):33-39.
36. Krents HB, Auld MC, Gill MJ. The high cost of medical care for patients who present late (CD4<200 cells/microL) with HIV infection. *HIV Med* 2004; 5: 93-98.