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The impact of liver disease: a leading cause of hospital admissions in people living with HIV

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ABSTRACT:

- **Background:** This study reviews recent trends of HIV inpatient admissions over 5 Infectious diseases Units in Liguria, in 2012.
- **Patients and Methods:** Five infectious diseases Units in Liguria, Italy, collected data on inpatient HIV admissions from January to December 2012, including patient demographic, discharge diagnosis, CD4 T-cell count, viral load (VL) and combined anti-retroviral treatment (cART).
- **Results:** Rate of patient admissions per 100 years was 6.12 (number=257), in 62.6% (n=161) of admissions a VL under 50 copies/ml was observed. Furthermore, 86.4% (n=222) of admissions were on active cART. Median age was 49 years. Mortality rate was 10.2%. Hepatitis C coinfection occurred in 64.6% of patients (n=166). The most common diagnosis was infectious diseases (29.1%), respiratory diseases (16.6%) and neoplasms (15.0%). Chronic HCV infection and its complications (cirrhosis and hepatocellular carcinoma) accounted for 31% of all discharging diagnosis.
- **Conclusions:** The majority of inpatients admitted during 2012 in our Units were on cART and virologically suppressed. The complications of hepatitis C coinfection have a major impact on mortality rates and hospitalization rates in Italy. According to these observations, the availability of new drugs for chronic hepatitis C imposes a further effort to improve the quality of life of our patients.
- **Key words:** Hospital admissions, Hepatitis C virus, HIV.

INTRODUCTION

The introduction of combined antiretroviral treatment (cART) has reduced HIV associated morbidity and mortality¹ as opportunistic infections rates have declined².

Yet the mortality rates remain three to fifteen times higher in patients living with HIV than those observed in the general population^{3,4}, since non infectious co-morbidities (NICMs) are becoming more apparent as the population starts to age⁵⁻⁸. This has been demonstrated in

studies of premature age-related comorbidities⁹ and higher hospitalisation rates amongst patients living with HIV compared to the general population¹⁰. The future impact of NICMs on patient care and service provision is still unfolding and information on current trends may be helpful in planning future services. The aim of this study is to describe the clinical characteristics and demographics of inpatient admissions in a net of Italian hospitals that provide dedicated HIV care.

PATIENTS AND METHODS

Four infectious disease Units (Sanremo, Galliera, San Martino, La Spezia) in Liguria, Italy, collectively known as the Analisi-Costi-Terapia-Antivirale network (ACTeA), were involved in the study. These centres were chosen due to their mutual interest and national universal health care systems.

Liguria accounts for about 700,000 inhabitants with 3,000 HIV patients attending one of the collective services. All hospital medical admissions of patients living with HIV from 1st January to 31st December 2012 were reviewed in this study. Surgical, paediatrics, obstetrics and gynaecological admissions were not included.

The ACTeA prospectively collected patient data via "The Ligurian HIV Clinical Network"¹¹, an online platform for collaborative studies in the field of HIV in Northwest Italy.

All centres coded admissions according the International Statistical Classification of Diseases (ICD) 9, and all Units have been standardised to allow comparison with the Z score formula. Only the principal clinical condition for hospitalisation was recorded by the lead clinical physician in the ACTeA or from the information recorded on discharge summaries. All data were anonymised and stored securely. Data categories collected for each patient are reported in Table 1.

For standardisation, viral loads below 50 copies/ml was included into the category of viral suppression according to Italian guidelines¹².

Data regarding cART were based on information from the last patient contact before the admission or on admission and were classified as: newly started (<6 months), stable (>6 months), poor adherence (if the adherence was below 80%, or clinicians had noted in the medical records or self-suspended), and failing regimen (if the patients required a switch of treatment).

For the opportunistic infections definition the following index diseases were used: *Cytomegalovirus* infection, *Toxoplasma gondii* encephalitis, *Pneumocystis jirovecii* pneumonia (PCP), pulmonary tuberculosis (TB), disseminated TB and TB lymphadenopathy, *Mycobacterium avium complex* (MAC) disease, *Cryptococcus* spp. infection, recurrent pneumonia (>2 episodes in one year)¹³.

ICD categories that reached a 3% threshold of total admissions were reviewed. Within each category, conditions that constituted 50% of the total ICD are discussed.

Fisher's exact or Pearson chi square test were used to compare categorical variables, while Mann-Whitney U test was used for continuous variables. Distribution of

Table 1. ICD9 codes.

ICD 9	Title
001-139	Certain infectious and parasitic diseases
140-239	Neoplasms
280-289	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
240-279	Endocrine, nutritional and metabolic diseases
290-319	Mental and behavioural disorders
320-359	Diseases of the nervous system
360-389	Diseases of the eye and adnexa
360-389	(diseases of the sense organs code related to eyes)
360-389	Diseases of the ear and mastoid process
360-389	(diseases of the sense organs codes related to ear)
390-459	Diseases of the circulatory system
460-519	Diseases of the respiratory system
520-579	Diseases of the digestive system
680-709	Diseases of the skin and subcutaneous tissue
710-739	Diseases of the musculoskeletal system and connective tissue
580-629	Diseases of the genitourinary system
630-679	Pregnancy, childbirth and the puerperium
760-779	Certain conditions originating in the perinatal period
740-759	Congenital malformations, deformations and chromosomal abnormalities
780-799	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
800-999	Injury, poisoning and certain other consequences of external causes

admission rate by country was estimated by negative binomial regression and the likelihood ratio test.

All analyses were performed with SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA: IBM Corp) and STATA (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX, USA: StataCorp LP).

RESULTS

A total of 257 admissions for 205 patients were identified (Table 2). The rate of patient admissions per 100 years was 6.12. The average number of admissions per patient throughout the one year period was 1.3, with a range of 1-7 admissions; 61.5% (n=126/215) of patients were coinfecting with Hepatitis C. The percentage of admissions with a CD4 count above 200 cells/ μ l was 68.1% (n=175). In 86.4% (n=222) of all admissions, the patient was on cART, in 62.6% (n=161) of admissions the most recent viral load was under 50 copies/ml. Among the patients on active cART (n=222): 73% (n=162) were on treatment for more than 6 months and 1.8% (n=4) had started cART less than 6 months prior to admission. Poor adherence was observed in 22% (n=49), a failing regimen was reported in 1.8% (n=4); self-suspension before admission occurred in 1.4% (n=3). The median viral load in non-suppressed patients (all patients on and off cART with VL RNA >50 copies/ml) was 4.36 log copies/ml.

Mortality rate of patients admitted during the study was 10.2% (n=21/205), a breakdown of discharge destinations is reported in Table 3.

Table 2. Cohort demographics

	IT n (%)
Total number of admissions	257
Total number of patients*	205
Gender (% based on total number of patients)	
– Female	58 (28.3)
– Male	147 (71.7)
Average age at spell*	
– Median	49
– IQR	45-53
Length of staying (days)	
– Mean average	16 (±14)
No of admissions which patients were on ARVs	222/257 (86.4)
Cd4 (cells/ml)	
– Median	302
– IQR	157-434
VL positive (copies/ml log ₁₀)	
– Median	4.36
– IQR	4.04-5.10
Route of infection* (% based on total number of patients)	
– Heterosexual sex	47 (22.9)
– Men who have Sex with Men	25 (12.2)
– Drug abuse	132 (64.4)
– Other/Unknown	1 (0.5)
Death (mortality rate) (% based on total number of patients)	21 (10.2)

*Each patients can have more than one hospital admission

Amongst the infectious and parasitic diseases admissions, the most commonly observed discharge diagnosis was chronic hepatitis C (n=32/257, 12.5%).

Pneumonia (with different codes merging on a single clinical diagnosis) was the leading respiratory disease, accounting for 10.5% (n=27/257) of cases. Hepatocellular carcinoma (n=19/257, 7.4%) was the most frequently described cancer. Liver cirrhosis (n=31/257 12.1%) was the most frequently recorded disease in the category of digestive systems. All details of discharging diagnosis are reported in Table 4.

DISCUSSION

In our study, the majority of patients who were admitted had a viral load below 50 copies/ml and 68.3% of admissions had a CD4 count above 200 cells/μl. This is related to the number of patients on cART at admission (86.4%),

Table 3. Outcomes.

	IT n=257
Usually	177 (68.9)
Died	21 (8.2)*
Hospice	0 (0.0)
Temporary	23 (8.9)
Other/Unknown	36 (14.0)

*Each patient may have more than one hospital admission before decease

with more than 50% of patients on cART for more than six months. Moreover, it suggests that the majority of admissions would not be AIDS-related, but due to other comorbidities. Chronic HCV was the leading cause of admission secondary to infection. This is consistent with the mode of HIV transmission in our cohort, as 64.4% were intravenous drug users¹⁴. The complications of HCV (including cirrhosis and hepatocellular carcinoma) were the most common cause of admissions (31%) and mortality (11.9%) in our cohort. The HCV data is in line with a well-established epidemiological scenario¹⁵. The prevalence of HCV coinfecting patients in the IT cohort is very close to the 45% reported by the Italian Cohort of Patients Naïve from Antiretrovirals (ICONA) in 2002¹⁶. Of importance, opportunistic infections are no longer the most common cause of admission secondary to infections and this crucial point is a clear sign of a changed epidemiology².

Pneumonia is associated with impaired immune status in HIV patients and recurrent pneumonias are considered an AIDS-defining event¹³. However, the aging HIV population is experiencing increased prevalence of chronic obstructive lung disease, with infection often being considered a trigger for exacerbations that might not simply be related to the immune system, but also to older patient demographic. Acute pyelonephritis are often related to sexual activity^{17,18}; especially among men having sex with men. This feature is deeply related to a changing pattern of HIV transmission in Italy¹⁹. Cardiovascular diseases are due to a well known-feature characterized by high prevalence of comorbidities⁹ and of major cardiovascular risk factors^{20,21}, so it is crucial to keep maximum attention to reduce the modifiable elements. The most frequently observed neoplasms (HCC, larynx and lung cancer) were not AIDS-defining cancers. This result is well aligned with the epidemiological picture drawn by Yaniket et al²², where the development of cancer is related with the time on cART. This data reflects the increased cancer risk with aging.

The rate of patient admissions per 100 years observed in our study (6) is lower than that observed in a similar study in Canada (21) in 2003²³, but this may be related to the improvements due to cART and HIV disease progression control. Duration of admission was longer than that reported by the European Community²⁴ for the Italian general population (8 days). However, with the complications of HCV coinfection rates in IT and the recognised impact on mortality^{25,26}, it is likely that the focus of care during these admissions is on severely unwell patients and end-of-life care, that would require a longer hospitalisation admission (average hospital stay 16 days). However, this could be improved with better community palliative care facilities, available in other European countries²⁷.

Future studies should consider identifying the number of new and follow-up diagnoses and cases for each patient admission, which may help to detect conditions that require further support or management in the community. Finally, these data do not reflect the whole national picture, only a local population, and therefore information regarding ethnicity groups and female patients is limited.

Overall, the patterns of these cohorts can help to iden-

Table 4.

Group	Commonest diagnosis	n=257(%)	Certain
Infectious and parasitic diseases	ICD 9 Codes	Clinical diagnosis	101 (39.3)
	070.54	Chronic Hepatitis c	32
	136.3	<i>P jrovecii</i> pneumonia	11
	130.0	<i>Toxoplasma gondii</i> meningitis	8
	042	HIV	7
	011.03	Tuberculosis of the lung	4
Neoplasms			47 (18.3)
	155.0	Hepatocellular carcinoma	19
	162.2	Lharynx cancer	6
	161.9	Lung cancer	4
	176.0	Kaposi's sarcoma	3
200.20	Burkitt's Lymphoma	2	
Diseases of the respiratory system			34 (13.2)
	486.0	Pneumonia	21
	481.0	<i>S.pneumoniae</i> pneumonia	3
	482.84	Pneumonia due to legionaires	1
	482.89	Pneumonia due to other specified bacteria	1
	483.0	Pneumonia due to mycoplasma	1
		Total Pneumonia	27
466.11	Acute bronchiolitis due to RSV virus	1	
Diseases of the digestive system			34 (13.2)
	571.5	Liver cirrhosis	31
	556.6	Ulcerative colitis	1
	558.9	Other non specified non infectious gastroenteritis	1
577.1	Chronic pancreatitis	1	
Diseases of the genitourinary system			8 (3.1)
	590.10	Acute pyelonephritis	3
	583.89	Other nephritis and nephropaties	1
	584.9		1
	592.0	Calculus of the kidney	1
604.90	Orchitis and epididimitis	1	
Diseases of the circulatory system			8 (3.1)
	428.0	Congestive Heart failure	2
	431.0	Intracerebral Hemorrhage	2
	401.9	Essential Hypertension	1
	410.30	Acute myocardial infarction of inferoposteior wall	1
	415.19	Other phlebitis and thrombophlebitis	1
Others			25 (9)

tify trends and patterns of HIV admissions in an aging population. The impact of hepatitis coinfection and malignancy needs major attention. Importantly, strategic planning of healthcare services needs to take into account the impact of NICMs in the future of HIV care. This is especially true today, that new drugs for HCV treatment are available, with the potential to improve the quality of life for our patients. This strategy could help saving on direct and indirect costs for the National Health Service.

CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998; 338: 853-860.
2. Mocroft A, Monforte Ad, Kirk O, Johnson MA, Friis-Moller N, Banhegyi D, Blaxhult A, Mulcahy F, Gatell JM, Lundgren JD; EuroSIDA study group. Changes in hospital admissions across Europe: 1995-2003. Results from the EuroSIDA study. HIV Med 2004; 5: 437-447.
3. Cockerham L, Scherzer R, Zolopa A, Rimland D, Lewis CE, Bacchetti P, Grunfeld C, Shlipak M, Tien PC. Association of HIV infection, demographic and cardiovascular risk factors with all-cause mortality in the recent HAART era. J Acquir Immune Defic Syndr 2010; 53: 102-106.
4. Zwahlen M, Harris R, May M, Hogg R, Costagliola D, de Wolf F, Gill J, Fätkenheuer G, Lewden C, Saag M, Staszewski S, d'Arminio Monforte A, Casabona J, Lampe F, Justice A, von Wyl V, Egger M. Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries. Int J Epidemiol 2009; 38: 1624-1633.
5. Weber R, Sabin CA, Friis-Møller N, Reiss P, El-Sadr WM, Kirk O, Dabis F, Law MG, Pradier C, De Wit S, Akerlund B, Calvo G, Monforte Ad, Rickenbach M, Ledergerber B, Phillips AN, Lundgren JD. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med 2006; 166: 1632-1641.
6. Justice AC. Prioritizing primary care in HIV: comorbidity, toxicity, and demography. Top HIV Med 2006; 14: 159-163.
7. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active an-

- tiretroviral therapy: New York City. *Ann Intern Med* 2006; 45: 397-406.
8. Phillips AN, Neaton J, Lundgren JD. The role of HIV in serious diseases other than AIDS. *AIDS* 2008; 22: 2409-2418.
 9. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, Berti A, Rossi E, Roverato A, Palella F. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011; 53: 1120-1126.
 10. Falster K, Wand H, Donovan B, Anderson J, Nolan D, Watson K, Law MG; Australian HIV Observational Database. Australian HIV Observational Database. Hospitalizations in a cohort of HIV patients in Australia, 1999-2007. *AIDS* 2010; 24: 1329-1339.
 11. Fraccaro P, Pupella V, Gazarara R, Dentone C, Cenderello G, De Leo P, Bozzano F, Casalino Finocchio G, De Maria A, Fenoglio D, Filaci G, Guerra M, Di Biagio A, Mantia E, Orofino G, Ferrea G, Viscoli C, Giacomini M. The ligurian human immunodeficiency virus clinical network: a web tool to manage patients with human immunodeficiency virus in primary care and multicenter clinical trials. *Med* 2013; 2: e5.
 12. Antinori A, Marcotullio S, Ammassari A, Andreoni M, Angarano G, Armignacco O, Carosi G, Cinque P, d'Arminio Monforte A, Di Perri G, Ensoli B, Florida M, Galli M, Mastroianni C, Matteelli A, Mazzotta F, Moroni M, Pal G, Puoti M, Puro V, Rizzardini G, Sagnelli E, Vella S, Vullo V, Lazzarin A; Italian HIV Guidelines Working Group. Italian Guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons. Update 2011. *New Microbiologica* 2012; 35: 13-159.
 13. [No authors listed]. MMWR 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992; 41: 1-19.
 14. Puoti M, Manno D, Nasta P, Carosi G. The burden of HIV and hepatitis C virus coinfection. *Curr Opin HIV AIDS* 2007; 2: 460-465.
 15. Andreoni M, Giacometti A, Maida I, Meraviglia P, Ripamonti D, Sarmati L. HIV-HCV co-infection: epidemiology, pathogenesis and therapeutic implications. *Eur Rev Med Pharmacol Sci* 2012; 16: 1473-1483.
 16. De Luca A, Bugarini R, Lepri AC, Puoti M, Girardi E, Antinori A, Poggio A, Pagano G, Tositti G, Cadeo G, Macor A, Toti M, D'Arminio Monforte A; Italian Cohort Naïve Antiretrovirals Study Group. Italian Cohort Naïve Antiretrovirals Study Group. Coinfection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naive HIV-infected subjects. *Arch Intern Med* 2002; 162: 2125-2132.
 17. Stapleton AE. Urinary tract infection pathogenesis: host Factors. *Infect Dis Clin North Am* 2014; 28: 149-159.
 18. Cenderello G, Tittle V, Pasa A, Dentone C, Artioli S, Setti M, Giacomini M, Fraccaro P, Viscoli C, Cassola G, Di Biagio A, Barbour A, Nelson M. Inpatient admissions of patients living with HIV in two European centres (UK and Italy); comparisons and contrasts. *J Infect* 2015; 14: S0163.
 19. Casari S, Suligoì B, Camoni L, Pavan A, Macchi L, Capelli M, Parainfo G, Compostella S, Castelli F, Carosi G, Donato F; NU.DI.H. Study Group. Epidemiological and clinical characteristics and behaviours of individuals with newly diagnosed HIV infection: a multicentre study in north Italy. *J Prev Med Hyg* 2012; 53: 190-194.
 20. De Socio GV, Martinelli L, Morosi S, Fiorio M, Roscini AR, Stagni G, Schillaci G. Is estimated cardiovascular risk higher in HIV-infected patients than in the general population? *Scand J Infect Dis* 2007; 39: 805-812.
 21. Bonfanti P, De socio GL, Marconi, Franzetti M, Martinelli C, Vichi F, Penco G, Madeddu G, Orofino G, Valsecchi L, Vitiello P, Menzaghi B, Magni C, Ricci E. Is metabolic syndrome associated to HIV infection per se? Results from the HERMES study. *Curr HIV Res* 2010; 8: 165-171.
 22. Yanik EL, Napravnik S, Cole SR, Achenbach CJ, Gopal S, Olshan A, Dittmer DP, Kitahata MM, Mugavero MJ, Saag M, Moore RD, Mayer K, Mathews WC, Hunt PW, Rodriguez B, Eron JJ. Incidence and timing of cancer in HIV-infected individuals following initiation of combination antiretroviral therapy. *Clin Infect Dis* 2013; 57: 756-764.
 23. Krentz HB, Dean S, Gill MJ. Longitudinal assessment (1995-2003) of hospitalizations of HIV-infected patients within a geographical population in Canada. *HIV Med* 2006; 7: 457-466.
 24. OECD (Organisation for Economic Co-operation and Development) annual report Health at glance: <http://www.oecd.org/els/health-systems/Health-at-a-Glance-2013.pdf> Last accessed 30 March 2014
 25. Crowell TA, Gebo KA, Balagopal A, Fleishman JA, Agwu AL, Berry SA. HIV Research Network. Impact of hepatitis coinfection on hospitalization rates and causes in a multicenter cohort of persons living with HIV. *J Acquir Immune Defic Syndr* 2014; 65: 429-437.
 26. Ananthakrishnan AN, McGinley EL, Fangman J, Saecian K. Hepatitis C/HIV co-infection is associated with higher mortality in hospitalized patients with hepatitis C or HIV. *J Viral Hepat* 2010; 17: 720-729.
 27. European Association for Palliative Care Atlas 2013 cartographic edition: <http://dSPACE.unav.es/dSPACE/handle/10171/29290?locale=en> last accessed 30 March 2014