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Number and characteristics of new HIV diagnoses in the Calabria Region and in one nearby centre in Messina: a resurgent or still hidden epidemic in Southern Italy?

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ABSTRACT:

Introduction: It is currently believed that Southern Italy (Calabria in particular) is less affected by the HIV epidemics than the rest of Italy. Detailed regional analyses are very important to define characteristics of HIV epidemics, across Italy and among different Italian regions. The impact of migration and socio-economical conditions may contribute to differences in prevalence and characteristics of new HIV diagnoses. This study aimed to describe the prevalence and the features of HIV-infected patients diagnosed in 2014-2015 in the Calabria Region and one nearby centre in Messina.

Patients and Methods: All new HIV diagnoses in all 7 Centers in the Calabria Region and 1 Centre in Messina, occurring between January 2014 and December 2015 were reviewed. Main demographical, virological, immunological and clinical data were recorded, as well as first-line antiretroviral regimens if prescribed.

Results: Ninety patients were selected. Most patients were males (78%) and Italians (73%). Migrants came more frequently from Africa (51%) and were concentrated in 3/7 Centers in the Calabria Region. Median age was 40 years (range: 20-71). More frequent risk factors for HIV acquisition were sexual intercourses (heterosexual [41%] or homosexual [39%]). Median CD4+ T-cell count at diagnosis was 342/mm^3 (range: 7-1163). Twenty-seven percent of patients had ≥1 AIDS events at or before HIV diagnosis; 49% were late presenters. Combination antiretroviral therapy (cART) was prescribed to 82% patient, whereas 14 patients who are currently on follow-up (all with CD4+ ≥500/mm^3 at diagnosis) have not yet started therapy. Twelve patients with an acute or recent infection received antiretroviral therapy.

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— ***Conclusions:*** Ninety new HIV diagnoses were found in 2014-2015. Importantly, we found a high prevalence of AIDS/late presenters. Centers acted with immediate cART for acute or recently infected patients, while the test-and-treat strategy recently recommended for patients with chronic HIV infection has not been applied yet in all cases. Southern Italy (Calabria in particular) merits attention as the burden of HIV is significant and clinical problems require maintenance and optimization of skills and resources.

— ***Keywords:*** HIV, AIDS, Epidemiology HIV, Migrants, Combination antiretroviral therapy.

List of abbreviations: HIV: human immuno-deficiency virus; AIDS: acquired immune deficiency syndrome; cART: combination antiretroviral therapy; MSM: men have sex with men; IDU: intravenous drug use; HCV: hepatitis C virus; HBV: hepatitis B virus; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor. TDF/FTC: tenofovir/emtricitabine; PI/r: protease inhibitor/ritonavir; AZT/3TC: zidovudine/lamivudine; ABC/3TC: abacavir/lamivudine; NNRTI: non nucleoside reverse transcriptase inhibitor.

INTRODUCTION

HIV epidemics and care may differ among Regions of the same Country, due to virus and host related conditions, but also to socio-economical heterogeneity. The impact of migration and poor socio-economical conditions of Southern Italian Regions may contribute to differences in prevalence and characteristics of new HIV diagnoses. Detailed regional analyses are very important to identify health priorities but data are lacking to guide appropriate decision-making processes by the Local Health Authorities and Clinicians.

The CalabrHIV cohort[1] is a regional observational prospective cohort created in 2014 and composed by all the Infectious Diseases Centers in the Calabria Region (2 Centers in Catanzaro, 1 in Vibo Valentia, 1 in Reggio Calabria, 1 in Cosenza, 1 in Crotone and 1 in Lamezia Terme). Five hundred forty-eight patients (68% males; 59% aged <50 years) on active follow-up as at October 2014 were previously included in the CalabrHIV Cohort[1]. Recently, a nearby centre in Messina (University of Messina) joined the Cohort.

A large number of patients with HIV infection included in the CalabrHIV cohort[1] suggested that the HIV/AIDS epidemics in the Calabria Region is more important than currently believed, although the last estimates of National Institute of Health reported the lowest incidence of new HIV diagnoses among Italian Regions[2]. Under- or late-reporting, under-testing due to the fear of stigma, marginalization of HIV-infected patients and "the health migration phenomenon" to areas of the North/Centre of Italy may have contributed to hide the HIV epidemics. At the same time, other factors (such as migration, or scarce knowledge about HIV prevention[3]) may have increased new HIV diagnoses.

So, a more update report about the prevalence of HIV infection in Calabria Region and Southern Italy is necessary. The present study aimed at exploring prevalence and characteristics of new HIV diagnoses occurred in the last two years (2014-2015) in the Calabria Region and one Centre in Messina (Sicily).

METHODS

All new HIV diagnoses in all seven Infectious Disease Centres belonging to the CalabrHIV Cohort in the Calabria Region and in one Centre in Messina (Figure 1) occurring between January 2014 and December 2015 were reviewed.

Patient characteristics were collected in a common electronic database. Main demographical, virological, immunological and clinical data were recorded, as well

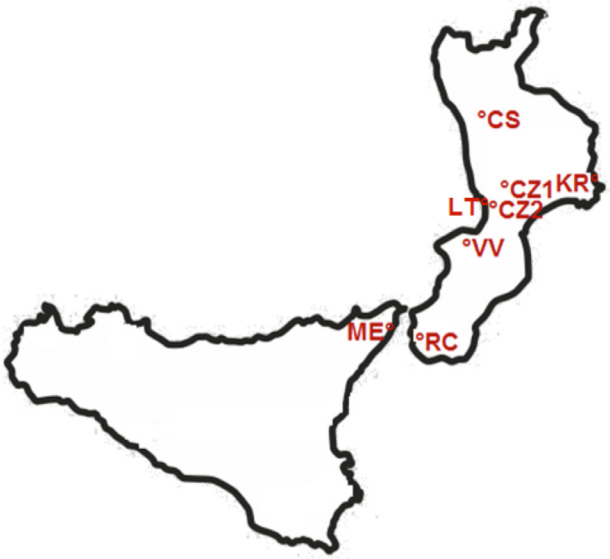

Figure 1. Map of CalabrHIV collaborating Centres (January-October 2014 and 2015). (Source: Ministry of Interior, 2016). *Legend:* CS: Unit of Infectious and Tropical Diseases, "Annunziata" Hospital, Cosenza; CZ 1: Unit of Infectious and Tropical Diseases, Department of Medical and Surgical Sciences, "Magna Graecia" University, Catanzaro; CZ 2: Unit of Infectious and Tropical Diseases, "Pugliese-Ciaccio" Hospital, Catanzaro ME: Unit of Infectious and Tropical Diseases, University of Messina; KR: Unit of Infectious and Tropical Diseases, "San Giovanni di Dio" Hospital, Crotone; LT: Unit of Infectious and Tropical Diseases, "Giovanni Paolo II" Hospital, Lamezia Terme, Catanzaro; RC: Unit of Infectious and Tropical Diseases, "Bianchi-Melacrino-Morelli" Hospital, Reggio Calabria; VV: Unit of Infectious and Tropical Diseases, "Jazzolino" Hospital, Vibo Valentia.

as first line antiretroviral regimens, if prescribed. For migrants, geographical areas of origin (Asia, East Europe, Africa, other nations) were recorded. Co-infections with hepatitis B virus (HBV) and/or with hepatitis C virus (HCV) were defined respectively, as HBsAg and/or HCV Ab positivity. Late presentation was defined as CD4+ T-cell count <350/mm^3 at diagnosis[4]. Recent HIV infection was considered as the phase up to 6 months after infection.

Patients with a first positive HIV test or first combination antiretroviral therapy (cART) prior to 1st January 2014 where excluded from the analysis, as well as those previously diagnosed in other Italian regions or abroad and actually under follow-up in the Calabria Region or the Infectious Disease Centre of Messina.

Comparison between migrants and Italian populations was performed. We used Wilcoxon-Mann-Whitney test for continuous variables and Chi-square test for categorical variables. *P*-value <0.05 was set for statistical significance.

RESULTS

Ninety new HIV diagnoses were recorded in the years 2014-2015. New diagnoses were rather concentrated in two Provinces, which covered 59% of them.

As shown in Table 1, most patients were males (78%) and Italians (73%). Median age was 40 years (range: 20-71). Median CD4+ T-cell count at diagnosis was 342/mm^3 (range: 7-1163). More frequent risk factors for HIV acquisition were sexual intercourses (heterosexual [41%] or homosexual [39%]). Intravenous drug users (current or past) were rare (5 patients overall) and a low prevalence of HCV-Ab seropositivity (7 patients among 83 tested) was found. HIV RNA load was available for 81/90 patients. Forty-two percent of them had HIV RNA ≥100,000 copies/ml before cART initiation. Twenty-seven percent of patients had ≥1 AIDS events at or before HIV diagnosis; 49% were late presenters. Fourteen percent of patients (n=13) had a recent or acute infection.

Table 1. Main characteristics of patients with a new HIV diagnosis in the study period

Qualitative variables	**N (%)**
Gender	
Males	70 (78)
Nationality	
Italian	66 (73)
Risk factors	
IVDU	5 (6)
Etero	37 (41)
MSM	35 (39)
Other/unknown	13 (14)
Co-infections	
HBsAg+	7 (8)
HCV Ab+	5 (6)
AIDS at diagnosis	23 (26)
Late presenters (CD4 T cell count <350/mm3)	44 (49)
Recent infection	13 (14)
Quantitative variables	**Median (range)**
CD4 + T cell count at diagnosis	342/mm^3 (7-1163)
Age	40 years (20-71)

Abbreviations: IVDU, intravenous drug use; MSM, men have sex with men.

Antiretroviral regimens were prescribed to 82% patients in the time-window of the study, including protease inhibitors (PI) in 42%, non-nucleoside reverse transcriptase inhibitors (NNRTI) in 13% and integrase inhibitors in 34% patients (Figure 2). Fourteen patients who are currently on follow-up have not yet started cART (all with CD4+ T cell count ≥500/mm^3 at diagnosis), one patient was lost to follow-up before cART prescription and one patient died. Twelve/13 patients with acute or recent infections received cART

Characteristics of migrants in comparison to Italian Caucasian patients

Twenty-four migrants were diagnosed in 2014-2015. Fifty-eight per cent (14 patients) were from Africa, 33% (8 patients) were from East Europe, 4.5% (one patient) was from Asia; for one patient geographic origin was not specified (Figure 2). Eighty-three per cent patients were in charge at only three Centres in the Calabria Region (in Crotone, Reggio Calabria and Cosenza Provinces).

Median age of migrants was 35 years (range 21-50) *vs.* 41 years (range 20-71) of Italian patients (p=0.181); median CD4+ T cell count at diagnosis was 366/mm^3 (range 7-1085) for migrants *vs.* 342/mm^3 (range 13-1173) for Italians (p=0.613). Differently from the Italian population, the percentage of females was higher (62.5% migrants *vs.* 7.5% Italians, p<0.001). Seventeen per cent migrants were co-infected by HCV and/or HBV *vs.* 11% Italians (p=0.437). Thirty per cent migrants *vs.* 29% Italians (p=0.972) had AIDS at diagnosis, and 30% migrants *vs.* 14% Italians (p=0.0884) have not yet received cART at the time of study closure.

DISCUSSION

This study evaluated prevalence and characteristics of new HIV diagnoses in the CalabrHIV cohort. Ninety new HIV diagnoses were actively recorded from Clinical Centres in 2014-2015. Importantly, to the twenty cases notified in the year 2014 to the National Institutes of Health[2], further fifty cases were added for the Calabria Region in the years 2014-2015. These numbers underline the somehow underestimated relevance of the HIV/AIDS epidemics in our context.

Patients were more frequently males, Italians and heterosexuals. In the majority of cases, patients were prescribed cART at or soon after diagnosis (82%). Indeed, test-and-treat strategies and anticipation of therapy at CD4+ T cell count ≥500/mm^3 improve patient survival[5], so more recent guidelines recommend to start HAART irrespectively of CD4+ T cell count at

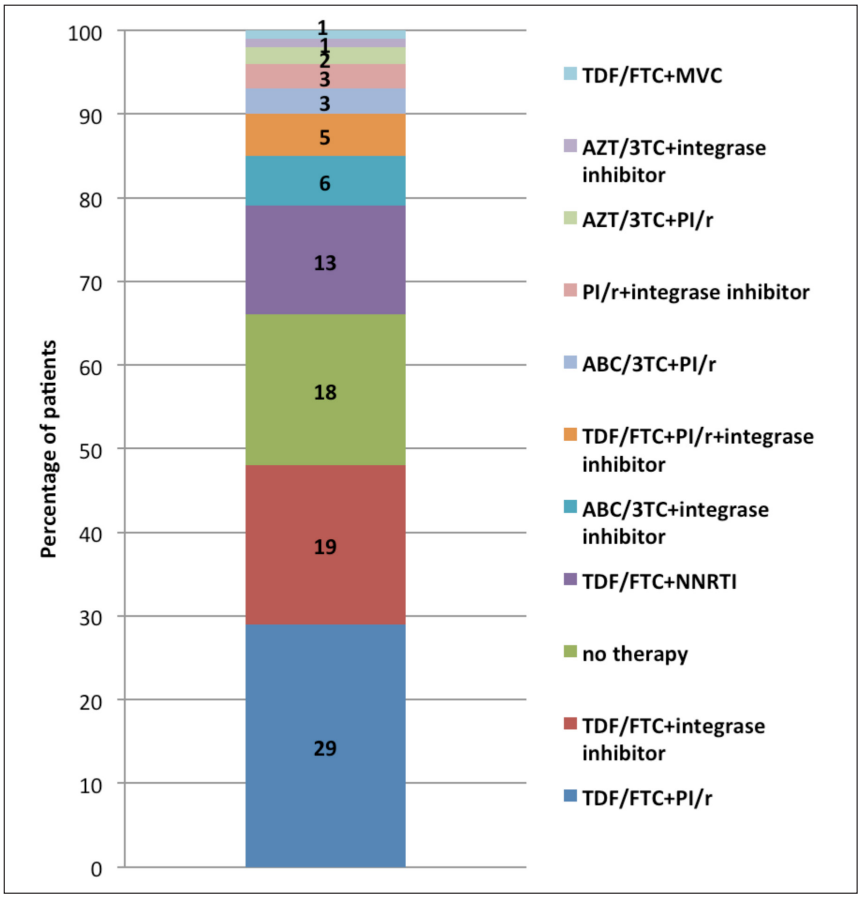

Figure 2. Status of combination antiretroviral therapy and first line prescriptions (frequency of patients is indicated in the y-axis).

diagnosis[6]. At the same time, early initiation of therapy contributes to decrease the risk of HIV transmission. All Centres acted with immediate cART for acute or recently infected patients, while the test-and-treat strategy recently recommended for patients with chronic HIV infection has not been applied yet in all cases (indeed some patients with CD4+ T cell count ≥500/mm^3 did not receive cART prescription). Therefore, our data show a good but not perfect adherence to the new guidelines[6]. Some factors may have contributed to a delay in cART initiation. Firstly, psychosocial issues (such as stigma still associated with HIV infection) may have increased patients' refusal. Secondly, retention in care of HIV-infected patients is affected by the massive phenomenon of "health migration" from the Calabria Region to other Regions in Northern/Central Italy where patients are prescribed cART.

A significant fraction of AIDS/late presentations was detected, similar to what recent European estimates have indicated[7]. Indeed, the rate of late presentation for 2010-2013 in Southern Europe was 45.8%[7], whereas we found 49% late presenters in our Cohort. Importantly, late presentation increases morbidity and mortality in HIV-infected patients and burden of HIV infections. Some factors may contribute to the late presentation. In some cases (as among heterosexual people), lack of knowledge, misuse of condoms and underestimation of risk of HIV acquisition may contribute to late diagnosis[8]. In other cases (as among foreign patients, migrants and IDUs) poor socioeconomic status, low educational level and poor access to health care may have contributed to delayed HIV diagnosis[9,10]. Consistently with recent National estimates[2] (that showed a decreased rate of new HIV diagnosis among IDUs from 2010 [6.6%] to 2014 [3.8%]) a lower rate of IDUs was found in our cohort than in previous years. This is also consistent with the low rate of co-infection with HBV and/or HCV found in our cohort.

A certain degree of heterogeneity among Centres for some characteristics (i.e., the proportion of migrants) was found. The proportion of migrants was higher in 3/7 Centres located in the Calabria Region (i.e. Reggio Calabria, Cosenza and Crotone Provinces) along the routes of migration towards coasts of Southern Italy and/or in the proximity of governmental Centres to host migrants and refugees in the Region. So, it is necessary to provide Centres that are mostly involved in the care of migrants with expertise, resources and diagnostic tools to allow early diagnosis and cure of both HIV and tropical diseases affecting this population.

Some differences in characteristics of migrants with respect to Italian patients were also found. We observed that migrants appeared younger than Italians, with a higher prevalence of AIDS at diagnosis and with a higher percentage of patients off cART (even though comparisons appeared to be not statistically significant). Importantly, the proportion of females was significantly higher among migrants than among the Italian population. We hypothesized that some new HIV diagnoses in women were obtained with screening during pregnancy. Indeed, screening HIV before or during pregnancy is important to prevent pediatric HIV infections thanks to a prompt cART initiation in pregnant women.

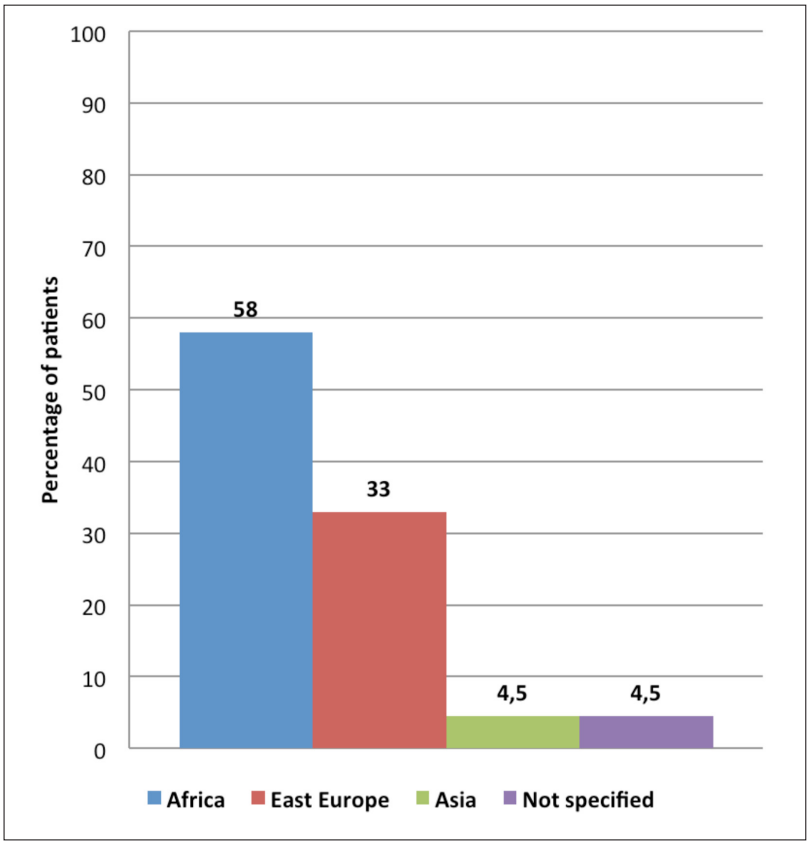

Figure 3. Geographic origin of migrants (N=24). *Legend:* Africa: 14/24 patients (58%); East Europe: 8/24 patients (33%); Asia: 1/24 patients (4.5%); Not specified: 1/24 patients (4.5%)

CONCLUSIONS

This work presents the most updated prevalence and characteristics of the new HIV diagnoses in our setting, after correcting for any delay in notification. Further studies have to elucidate possible differences in characteristics of the HIV epidemics in our Regions with respect to the Northern-Central part of Italy and with respect to other Southern Italian Regions. A network among Southern Italian regions would, therefore, be desirable, to recognize health priorities, optimize health services and implement screening strategies in Southern Italy. Overall, HIV infection appears to be more important in our Region than currently believed and we believe that more efforts and resources should be dedicated to HIV disease management in our setting.

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Conflict of Interests:
The Authors declare that they have no conflict of interests.

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