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Original Article

Immunological Evolution of a Cohort of HIV-2 Infected Patients: Peculiarities of an Underestimated Infection

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Abstract. ***Background:*** **Human Immunodeficiency Virus type 2 (HIV-2) affects a minority of patients in Italy; nevertheless, the increasing migratory flow from higher prevalence areas led to the spread of this virus into our Country. We evaluate clinical, viro-immunological, and therapeutic characteristics of patients with HIV-2 infection and HIV-1/HIV-2 dual-infection and the early treatment impact on overall survival and incidence of AIDS events.**
Methods: **We retrospectively analyzed all HIV-2, and HIV-1/HIV-2 positive patients followed in a large Italian clinic from January 1987 to December 2020. We recorded demographic, viro-immunological, clinical, and therapeutic data. We performed a descriptive analysis followed by a longitudinal analysis to explore the factors associated with the CD4+ lymphocyte trend; lastly, we studied the possible predictors of death and AIDS in our cohort in a multivariable model.**
Results: **32 subjects were enrolled, 17 (53%) HIV-2 infected and 15 (46.8%) HIV-1/HIV-2 dual-infected; 12 patients were lost to follow up, while 3 died. We found a lack of HIV-2 viremia in 12/32 subjects (37.5%). Most of the patients at baseline had a good viro-immunological profile with HIV-2 RNA <200 copies/ml and CD4+ lymphocyte >200 cell/mcl. We found a CD4+ lymphocyte improvement over time, both in the absolute number (β 472.61, 95%CI 383.05-562.18, p<0.001) and in percentage (β 25.28, 95%CI 21.91 – 28.66, p<0.001). Nevertheless, subjects taking cART had CD4+ lymphocyte percentage increase over time, and this trend appeared significantly better than those who did not receive therapy. Lastly, in the multivariable model CD4+, T-cell count increase was negatively associated with AIDS (HR 0.34 95%CI 0.13-0.91, p=0.032).**
Conclusion: **We found a higher prevalence of HIV-1/2 dual infection than in previous observations. Subjects with HIV-2 infection showed a favorable immunological condition at diagnosis, and the benefits of cART in those who received treatment are undiscussed. Moreover, our data suggest a different disease course based on age at diagnosis, as in HIV-1 infections. We encourage starting cART at diagnosis in HIV-2 patients, regardless of CD4+ lymphocyte, because even in the new cART era, CD4+ lymphocyte decrease remains the strongest predictor of death and AIDS also in this population.**

Keywords: HIV-1, HIV-2, AIDS, Italy, cART.

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Introduction. In 2019 the World Health Organisation (WHO) estimated that HIV infection affected approximately 38 million people worldwide.[1] Most of the statistics are built based on data of HIV-1 infection; however, HIV-2 is very peculiar for its epidemiological, virological, and clinical characteristics. It started as a zoonosis from the SIV of the sooty mangabey.[2,3]

To date, at least nine groups of HIV-2 have been described (termed A-I), with groups A and B being the most prevalent and the only two groups that have continued to transmit from person to person.[4,5]

The two viruses have similar transmission routes and cellular targets, but HIV-2 remains much less transmissible than HIV-1 and shows differences in the natural history of infection.[6,7]

Because of the lower prevalence and the less virulence of HIV-2, accurate estimates on the number of cases are lacking. By crude estimates, in the 1990s, one or two million patients were infected with HIV-2.[8,9] In the United States of America, to enumerate and describe HIV-2 cases, a working case definition was developed, and, during 1988 - June 2010, a total of 242 HIV-2 cases were reported to CDC.[10] In Italy there is a lack of systematic informations about the epidemiology of this infection.[11] HIV-2 prevalence has declined in several West African countries during the last two decades, but the reasons are unclear.[12]

Dual HIV-1 and HIV-2 mixed infections have been reported mostly in West Africa, where the two viruses are endemic (HIV-2) and epidemic (HIV-1) and where it is estimated that approximately 5-10 percent of HIV-1 infected individuals are coinfected with HIV-2.[13]

Limited data exist on the natural history of HIV-1/ HIV-2 mixed infections. However, a meta-analysis performed in 2014 showed no evidence that HIV-2 delays progression to death in HIV-1/HIV-2 coinfected patients,[14] and initial infection with HIV-2 does not appear to protect against a subsequent HIV-1 acquisition.[15] On the other hand, one study suggests that people with both viruses have a slower progression of the disease and a delayed death when compared with people who have HIV-1 alone, with the greatest benefits when HIV-2 infection occurs earlier than HIV-1.[16]

Several studies showed that HIV-2 is generally less pathogenic than HIV-1, with a longer asymptomatic stage of infection, a slower decline of CD4 T-cell count, and a lower level of plasma viremia.[17]

There are no antiretroviral medications approved by the US Food and Drug Administration for HIV-2, and the selection of combination antiretroviral therapy (cART) for these patients appears to be complicated because of the lack of randomized clinical trial data giving indications on when to start and on the choice of initial or subsequent cART regimens. In fact, all the antiretroviral therapies have been developed against HIV-1, and many are inactive against HIV-2. HIV-2 is intrinsically resistant to the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the fusion inhibitor, enfuvirtide. Moreover, the only protease inhibitors active against HIV-2 are lopinavir and darunavir, both boosted by ritonavir or cobicistat. International guidelines[18] suggest starting the antiretroviral treatment in HIV-2 infected patients with an integrase inhibitor (INI) plus 2 NRTIs or, as a second-line regimen, to choose boosted protease inhibitors (PIs) active against HIV-2 plus 2 NRTIs.

The existing data suggest starting antiretroviral therapy at or soon as the diagnosis of HIV-2 infection is made to prevent disease progression and transmission of HIV-2 to others.[18]

Physicians need to face some problems when making decisions about patients living with HIV-2 infection. The first one is the lack of standardized guidelines for HIV-2 infection treatment; the decision to start therapy is not methodical because of the lower virulence, and the minor damage HIV-2 can cause to the host. In addition, plasmatic viremia is often not detectable or very low, even without any treatment. The lack of cohort of patients with HIV-2 infection is another issue; the available literature is set up on study with a few patients, and data are fragmented and often set up as case reports, not as real observational studies.

The aim of this study is to evaluate clinical, viro-immunological, and therapeutic characteristics of a cohort of patients with HIV-2 infection and HIV-1/HIV-2 co-infection and to assess the treatment impact on the viro-immunological conditions and incidence of AIDS events.

Methods. The present was a retrospective, observational single-center study. We analyzed all ART-naïve, and ART-experienced HIV-2 infected, and HIV-1/HIV-2 coinfected adult patients followed at the outpatient Clinic of Infectious and Tropical Disease Department, University of Brescia and ASST Spedali Civili Hospital of Brescia, Italy, from January 1987, when patients were included in our cohort, to December 2020.

Data were retrieved from medical records and included gender, age, medical history, risk factors for HIV acquisition, viro-immunological characteristics including CD4+ T-cell, CD8+ T-cell, CD4+/CD8+ ratio, plasma HIV-1 and HIV-2 viral load, presence of single HIV-2 infection or HIV-1/HIV-2 co-infection, antiretroviral regimen prescribed, therapy starting year

and presence of AIDS event. After initiation into care, patients were typically followed every six months. Patients' outcomes included death, loss to follow-up, or still in care.

HIV-2 was diagnosed through WB and/or immunoblotting in case screening test was suspected of HIV-2 infection. HIV PCR was required, if available, in case of HIV-2 positive WB or in patients coming from endemic areas with characteristics compatible with HIV-2 infection.

HIV 1 and 2 viral loads were detected with biomolecular methods that changed during the observational time. HIV-1 RNA was detected with Versant HIV-1 RNA 1.5 Assay (kPCR) from 1997 until the end of the data collection. For HIV-2 RNA, the first commercial test used by our laboratory was HIV-2 Real-Time RT-PCR Kit, followed from 2014 by Human Immunodeficiency Virus type 2 genesig Standard Kit. We divided our sample in two groups: patients with HIV-2 infection (*Group 1*) and patients with HIV-1 and HIV-2 mixed infection (*Group 2).* We compared the two groups and assessed whether there was any significant difference between viro-immunological conditions, demographic characteristics, number of AIDS events, and antiretroviral treatment received. Regarding HAART, we compared whether there was any difference in the viro-immunological conditions between subjects who started therapy and those who did not.

A *favorable viro-immunological profile* (FP) was defined as the simultaneous presence of a CD4+ T-cell count > 200 cells/μL and an HIV2 RNA < 200 cp/ml, while any other combination defined a *non-favorable viro-immunological profile* (nFP). *Early treatment start* was defined as the initiation of cART within one month from the diagnosis of HIV-2 infection.

Statistical analysis. Continuous and categorical variables were summarized by the median and interquartile range and by count and percentages. A Kruskal-Wallis test was applied for continuous variables, while a chi-square test was performed for categorical variables to look at differences between Group 1 and Group 2. A linear mixed effect model was then applied to test for the trend over time of CD4+ lymphocyte (absolute and percentage) between age and therapy groups. We finally fitted a Cox proportional hazard regression model to test for the effect of CD4+ lymphocyte, age, and therapy on time to death and AIDS events.

Ethics. This study was approved by the Ethical Board of Brescia Provence and conducted according to the Declaration of Helsinki and to principles of Good Clinical Practice (GCP). As this study had a retrospective design and was based on routinely collected data, patients' informed consent was not required according to the Italian law (Italian Guidelines for classification and conduction of observational studies, established by the Italian Drug Agency, "Agenzia Italiana del Farmaco – AIFA" on March 20, 2008). Moreover, for this study, we used the general authorization of the Italian Guarantor for the use of retrospective demographical and clinical data, which have been anonymized and treated according to current Italian laws.

Results. In our study, we enrolled 32 patients (47% female), 17 (53%) with HIV-2, and 15 (46.8%) with an HIV1/HIV2. During the observational period, 12 patients were lost to follow-up after a median of 8 years, while 3 died. The baseline characteristics of our population are summarized in **Table 1**.

Demographic characteristics. The mean age and sex of patients of the two groups were similar, with 39.3 years old (IQR 28.2 - 47.7) and 58.8% males in the mono-infected group and 39.2 years old (IQR 34 - 43.6) and 46.7% males in the other group.

Twenty-seven patients (84.4%) came from Africa, 13 with HIV-2 infection and 14 with co-infection with HIV-1. We had no South American or Caucasian patients with HIV-2, and just 15.6% (5/32) came from Asia, two with co-infection and three with HIV-2 infection.

Viro-immunological profile and AIDS events. We found a lack of HIV-2 viremia at baseline in 12/32 (37.5%) subjects. However, between the 20 patients with an available HIV-2 RNA value at baseline, we did not find any significant difference between the viro-immunological conditions of the two groups: we found a similar proportion of subjects with a *favorable viro-immunological profile* [8/17 (47%) in the mono-infected group and 5/15 (33.3%) in the coinfected group]. At baseline, males had a lower CD4/CD8 ratio (mean CD4/CD8 ratio, 0.52 vs 0. 96, P=0.048) than females.

Likewise, at baseline we found a similar median number of CD4+ T-cell between HIV-2 and HIV-1/HIV-2 coinfected patients [percentage, 28 % (IQR 8 - 32.9) vs 23.8 % (IQR 16.1 – 26.7), p=0.462; absolute, 464 cell/mcl (IQR 111 - 704) vs 381 cell/mcl (IQR 204 - 629), p=0.955]. Regarding CD8+ T-cell value, patients infected by both viruses had a higher value of absolute CD8+ T-cells [median CD8+ 1029 cell/mcl (IQR 863 - 1201) vs 566 cell/mcl (IQR 447 – 768), p=0.001].

Only two patients of Group 1 developed AIDS defining illnesses: one developed *Pneumocystis jirovecii* pneumonia and the other was diagnosed with chronic intestinal isosporidiosis; in both cases, the diagnosis was made when they were first diagnosed with HIV infection. A similar percentage was found in the coinfected group: one patient developed only one AIDS event (pulmonary tuberculosis), two developed two AIDS-defining events (one pulmonary tuberculosis and non-Hodgkin lymphoma, and the other one disseminated

Table 1. Demographic and viro-immunological characteristics of the study cohort.

Demographic characteristics	Group 1 HIV-2 (n=17)	Group 2 HIV1/HIV2 (n=15)	P value
Age, median (IQR)	39.3 (28.2 – 47.7)	39.2 (34.1 – 43.6)	0.777
Female, n (%)	7 (41.2)	8 (53.3)	0.492
Ethnicity, n (%)			
- Caucasian	0 (0)	0 (0)	
- African	14 (82.4)	13 (86.7)	
- Asian	3 (17.6)	2 (13.3)	
Risk factors, n (%)			
- DA	0 (0.0)	0 (0)	
- Eterosex	12 (70.6)	14 (93.3)	
- Omosex	0 (0.0)	0 (0)	
- Unknown	5 (29.4)	1 (6.7)	
HIV characteristics at baseline			
Miss, n (%)	3	9	
HIV-2 RNA cp/ml, mean (±SD)	8387 (± 26479)	291 (± 714)	0.334
HIV-1 RNA cp/ml, mean (±SD)	NA	21065.11 (± 55952.3)	NA
CD4+ value			
- CD4+ /mcl, median (IQR)	464 (111 – 704)	381 (204 – 629)	0.955
- CD4+ %, median (IQR)	28 (8 – 32.9)	23.8 (16.1 – 26.7)	0.462
CD8+ value			
- CD8+/mcl, median (IQR)	566 (447 - 768)	1029 (863 - 1201)	0.001
- CD8+%, median (IQR)	34.7 (33.2 – 55.1)	48.5 (44.7 – 52.5)	0.160
CD4/CD8 ratio, median (IQR)	0.8 (0.1 – 1)	0.5 (0.4 – 0.7)	0.588
AIDS, n (%)	2 (11.7)	3 (20)	0.645
Viro-immunological conditions, n (%)			
- HIV-2 RNA >200 cp/ml and CD4+ < 200/mcl	2 (11.7)	0 (0)	0.524
- HIV-2 RNA <200 cp/ml and CD4+ > 200/mcl	8 (47.1)	5 (33.3)	
- Others	7 (41.2)	10 (66.7)	

DA: drug addiction, NA: not applicable

cytomegalovirosis and neurotoxoplasmosis).

Antiretroviral therapy. In our cohort, six patients (18.7 %) never started therapy (five with HIV-2 infection and one with HIV-1/HIV-2 co-infection), five of whom were lost to follow up after a median of 8 years (IQR 4.5-15) from diagnosis. At baseline, they all had a favourable viro-immunological status compared to those who started it, a significant higher value of CD4+ lymphocyte, both absolute [median CD4 762.5 cell/mcl (IQR 712.5-867.3) vs 324.5 (87.8, 538.3), p<0.001] and percentage [42.6% (IQR 33.7-47.875) vs 21.8 (9.9-27.4), p<0.001], and a significant higher CD4+/CD8+ ratio [1.4 (IQR 1-1.8) vs 0.5 (0.16-0.8), p=0.02]. Their viro-immunological status remained favorable during the time, and they never developed any AIDS event.

Twenty-six patients started therapy during the observational period, seven of whom were lost to follow-up after a median of 7 years (IQR 2-12) from diagnosis. They were all under treatment at the last visit of follow-up recorded. Of those who started therapy, eight patients (30.1%) started treatment within one month from diagnosis (*early treatment*). Among those who did not experience an *early treatment*, most (66.7%) started HAART later than 6 months from diagnosis. The most used first-line cART regimen was a protease-inhibitor (PI) based regimen, chosen for 8/12 HIV-2 patients and 7/14 HIV-1/HIV-2 coinfected patients on cART (**Table 2**). The most frequent PI-based regimen was lopinavir-ritonavir, prescribed in 3/12 (25 %) HIV-2 patients and 2/14 (14.3 %) HIV-1/HIV-2 coinfected patients on cART.

NNRTIs were chosen for 3/14 (21.4%) HIV-1/HIV-2 coinfected patients: one started with 2 NRTIs plus

Table 2. Antiretroviral therapy regimen.

	Group 1 (N=17)		Group 2 (N=15)	
	ARV-naive (n=5)	ART (n=12)	ARV-naive (n=1)	ART (n=14)
2NRTIs*+PI, n (%)	NA	8 (66.7)	NA	7 (50)
3NRTIs, n (%)	NA	0 (0)	NA	0 (0)
2NRTIs+NNRTI, n (%)	NA	0 (0)	NA	3 (21.4)
2NRTIs+INI, n (%)	NA	4 (33.3)	NA	3 (21.4)
2NRTIs, n (%)	NA	0 (0)	NA	1 (7.1)

NRTI: Nucleos(t)ide Reverse Transcriptase Inhibitors; NNRTI: Non-Nucleos(t)ide Reverse Transcriptase Inhibitors; INI: Integrase Inhibitors; PI: Protease Inhibitors; NA: not applicable

efavirenz, and two started with 2 NRTIs plus nevirapine. Two of them improved their immunological conditions during the follow-up, while one remained stable. None of them developed any AIDS-defining conditions.

None of the HIV-2 mono-infected group started with an NNRTI-based or an NRTI-based regimen. An INI-based regimen was chosen for 4/12 (33.3%) HIV-2 infected and 3/14 (21.4%) HIV-1/HIV-2 coinfected patients on cART. The most prescribed backbone regimen in HIV-2 infected patients was tenofovir disoproxil or tenofovir alafenamide plus emtricitabine, initiated in 10/12 (83.3%) patients. In HIV-1/HIV-2 coinfected patients, the most frequent first-line backbone regimen was represented by zidovudine plus lamivudine (42.9%).

Even though the immunological status of the untreated patients remained *favorable* over time, we noted that both CD4 absolute and CD4 percentage counts in subjects who started therapy showed an increasing trend over time compared to those who did not start it. The difference of the trends over time between the two groups was statistically significant (CD4 +: beta 18.96, 95% CI 8.56 - 29.36, p <0.001; CD4% beta 1.12, 95% CI 0.84 - 1.40, p <0.001) (**Figure 1**).

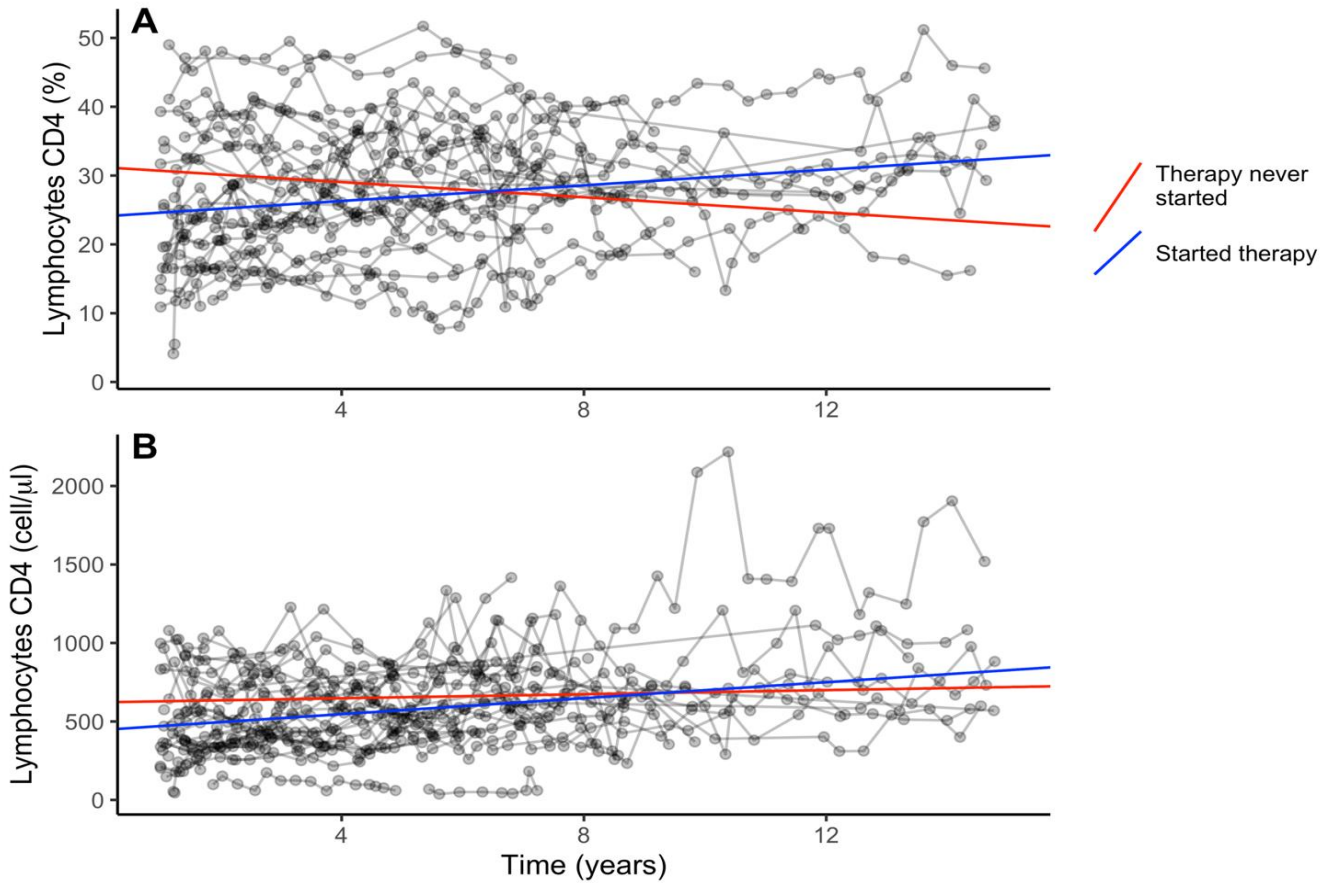
Lastly, as we expected, in the multivariable model, CD4+ T-cell count increase was negatively associated to AIDS (HR 0.34 95%CI 0.13-0.91, p=0.032).

Discussion. In this study, we found that the benefits of cART are undiscussed even in patients with a favorable viro-immunological condition at baseline. As in HIV-1 patients, CD4+ lymphocyte reduction remains the strongest proxy of death and AIDS also in this population.

At our outpatients' Clinic, in 2020 we were following 3875 patients with HIV infection. Despite this number, we could find only a small percentage of HIV-2 infections or HIV-1/HIV-2 co-infection patients. That is in line with what literature tells us about the distribution of this infection globally, with most patients living in West Africa with a limited spread to other regions.

Data estimate that in West Africa 5 to 10 percent of HIV-1 infected individuals are coinfected with HIV-2.

However, in our Clinic, as we would expect in a European hospital, we found only a minimum number of HIV-1 and HIV-2 coinfected patients (0.4 %), and most of them were coming from Africa.



	Graphic A		Graphic B	
Predictors	*Estimates (CI 95%)*	*p*	*Estimates (CI 95%)*	*p*
Patients who started therapy	-0.55 (-0.81 – 0.29)	<0.001	6.52 (-2.89 - -15.94)	0.175
Patients who started therapy	1.12 (0.84-1.40)	<0.001	18.96 (8.56 – 29.36)	<0.001

Figure 1. CD4 lymphocytes trend in cART-naive and in cART-experienced patients.

We did not find any relevant difference in demographic and viro-immunological characteristics between HIV-2 patients and HIV 1-2 coinfected patients.

Full amounts of data regarding HIV-2 infection are lacking. Immunoblot antibody tests used to confirm HIV reactive screening tests did not contain reagents specific to HIV-2 and, thus, were not reliable for identifying HIV-2 infections.[19] Serological tests do not distinguish between HIV-2 and HIV-1 infection, and, especially in patients infected with both viruses, when the clinical suspicion is not high, HIV-2 infection could be underestimated. Additional testing specific to HIV-2 infection should be considered if HIV-1 test results appear to be atypical or inconsistent with clinical findings, especially if patients come from endemic Countries. Dual infection can be proven by the presence of HIV-2 and HIV-1 DNA or RNA by PCR isolation of both viruses, but plasma HIV-2 RNA may be undetectable, and HIV-2 proviral DNA may be low or quickly negative in some persons, making confirmation of HIV-2 infection difficult.[20]

An early diagnosis is particularly important as HIV-2 results intrinsically resistant to some drugs that are normally used to treat HIV-1 infection, and late recognition of HIV-2 infection could lead to a delayed start of the correct therapy.

Regarding patients with HIV-1 and HIV-2 co-infection, we found that three patients started treatment with an NNRTI-based regimen, known to be ineffective against HIV-2. We think that this choice was made for misdiagnosis of HIV-2 infection. Nonetheless, they all maintained a virological suppression during the time and had an increase in the CD4+ T-cell count. One of them died after two years due to a non-AIDS-related event, while the other two subjects switched the cART regimen due to toxicity.

Although patients with HIV-2 infection seem to have a slower CD4+ lymphocyte decline and a slower disease progression, we notice that those who were taking cART had a CD4+ lymphocyte percentage increase over time and that the CD4+ T-cell count increase was negatively associated with death or AIDS, as we usually see in HIV-1 mono-infected individuals.

We encourage starting cART at diagnosis in HIV-2 patients, regardless of CD4+ lymphocyte, because even in the new cART era, CD4+ lymphocyte decrease remains the strongest predictor of death and AIDS also in this population.

The study's limitations are the lack of data regarding HIV-2 in patients diagnosed before 2000th, the observational retrospective design of the study, and the diagnostic technique that are changed during the observational period.

Conclusions. This study confirmed the benefits of antiretroviral therapy in those who received cART and demonstrated that the failure to initiate treatment significantly reduces the circulating CD4+ T cells over time, increasing the risk of death and AIDS-defining events development. These findings are important in patients with HIV-2 infection, where the clinical evolution and worsening of the viro-immunological parameter are often underrated.

As in HIV-1 infected patients, the decrease in CD4 T-cells remains the strongest indicator of death and AIDS events in this population. We can also confirm the importance of regular follow-up for these patients, with periodic control of viremia and CD4+ lymphocyte.

Considering the continuous migratory flows from regions where HIV-2 is endemic, the small number of patients, and the lack of some data regarding HIV-2, it will be necessary to carry out further studies, preferably multicentre and using standardized diagnostic techniques, to characterize this infection better.

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