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The access to the viral tropism test and the effectiveness and tolerability of treatment with the CCR5 coreceptor inhibitor Maraviroc (MVC). An observational retrospective multi-centre study in an HIV+ Sicilian population

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ABSTRACT: Maraviroc (MVC) is the first CCR5 inhibitor licensed for clinical use. A pre-treatment test is mandatory to identify the viral tropism of HIV+ patients. Different phenotypic and genotypic methods have been used to identify viral tropism. The aim of this observational retrospective study is to categorize the reasons and the results of tropism test and to evaluate efficacy and tolerability of MVC based regimens in a group of multi-experienced patients.

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The clinical records of 213 HIV+ subjects from 15 Infectious Diseases Units in Sicily that were screened for tropism test were reviewed for age, sex, risk, clinical stage (CDC, CD4 cell count, HIV RNA viral load), therapeutic line, indication and result of test for viral tropism. Within subjects treated with MVC, HIV RNA, CD4 cell count and metabolic parameters trend (measured at time 0 and then at month 4, 8, 12, 16, 20, 24), and adverse event were analyzed. Between January 2008 e December 2011, 213 subjects were screened with Trofile™ or genotypic tropism tests. 200 (92.6%) subjects were on HAART. The others were naive or on treatment interruption. 119 (56%) of screened subjects were CCR5 tropic. We observed a lower number of undetermined test with genotypic test vs. Trofile (2.7% vs. 15.9%). To be R5, D/M or X4 tropic wasn't associated with motivation to perform the test, therapeutic line, CD4 cell count, HIV RNA and CDC stage. 76 subjects (35.7%) were treated with MVC, 72 out of 115 CCR5+(62.6%). After 12 months of treatment with a MVC based regimen, 56.8% (ITT analysis) and 61.7% (AT analysis) of patients had HIV RNA <50 copies/ml. Median CD4 cell count was 387 (IQR 218-455) cells/µl. After 24 months of treatment with a MVC based regimen, 64.8% (ITT analysis) and 80% (AT analysis) of patients had HIV RNA <50 copies/ml. Median CD4 cell count was 381 (IQR 222-515) cells/µl with a median increase of 168 (IQR 54-274) cells/µl. Seven subjects stopped the treatment: two patients died, one had an adverse event, four had virological failure, three of them with low adherence. New drugs used in MVC based regimen were mainly darunavir and raltegravir. 42% of new combinations were NUCs sparing. An high number of multi-experienced subjects treated with a MVC based regimen obtained HIV RNA <50 copies/ml and a satisfactory increase of CD4 cell count. MVC was generally well tolerated with a good metabolic profile.

BACKGROUND

Gp120 is a capsidic protein of the HIV virus that interacts with the CD4 receptor of the target cell. Other cellular co-receptors are involved in this phenomenon, such as the chemokine receptors CCR5 and CXCR4[1]. The HIV virus is able to use both receptors; the ability to use alternatively one of them or both at the same time (dual or mixed D/M) by the different viral strains is defined tropism[1,2].

R5 strains are present at the time of transmission of the virus and it is estimated that about 80% of untreated subjects present an R5 tropism[1-3]. Bon et al[3] showed a high prevalence of R5 viral strains in multi-experienced patients.

Maraviroc (MVC) is an antagonist of CCR5 and is able to bind to the human chemokine receptor CCR5 preventing HIV entry into the cells. The CCR5 inhibitors are the only drugs that act on a cell target and not on a viral one: at present, since not all functions of CCR5 in the immune response are well-defined, the effects of long-term inhibition of the CCR5 co-receptor are not yet known[1-3].

Maraviroc (Celsentri®) is the first inhibitor of HIV entrance in CD4 + cell, indicated for oral use, in combination with other antiretroviral agents, for the treatment of adult subjects with an HIV-1 infection caused by a CCR5 tropic strain[1-3]. The clinical efficacy of MVC in optimized combination with other antiretroviral has been demonstrated in several double-blind randomized clinical trials[4-7]. The drug seems well tolerated and discontinuation of treatment due to adverse events appears comparable to the control group. In particular, the experimental clinical trials conducted head to head with efavirenz demonstrated the non-inferiority of the arm ZDV/3TC + MVC versus the control group, fewer side effects and treatment interruption, a more favourable metabolic profile and especially a more significant increase in CD4 lymphocytes[4-6]. Moving to real life study, Rossetti et al[8] showed that a significant proportion (65.4%) of experienced patients treated with regimens containing MVC achieved HIV-1 RNA < 50 copies/ml. Dentone et al[9], in an Italian multicenter observational study, confirmed that patients treated with MVC achieve a CD4 count >350/mmc and an undetectable HIVRNA in 9-12 months. On the contrary, MVC intensification in immunological non responders doesn't seem to produce a significant advantage in reconstituting CD4 T-cell pool, while it does substantially expand CD8 T-cells[10,11].

This is partly in contrast with the fact that patients treated with MVC tend to have a more rapid decrease in CD38 expression on CD4 lymphocytes, while the decrease of CD38 on CD8 cells correlates with the increase in CD4 lymphocytes. The mechanism underlying the greatest increase in CD4 is not completely clear[5,7].

The effect of MVC on some inflammation markers suggests a potential direct effect on immune activation and inflammation. In treated patients, in fact, the D-dimer levels tend to decrease more rapidly, while the C-reactive protein remains stable. At present, intensification clinical studies performed in patients with undetectable plasma viremia and discordant immunologic response (immunological non-responders) do not seem to provide exciting results[6].

Finally it was suggested that adding MVC to an effective ARV regimen in patients with HIV-HCV co-infection can lead to lower levels of liver fibrosis and there is no evidence of excess hepatotoxic effects[12]. Furthermore, more patients in whom maraviroc failed had a virus binding to the CXC chemokine receptor (CXCR4) at failure, but there was no evidence of a decrease in the CD4 cell count[8]. Anyway, data from clinical studies conducted to date appear discordant[12,13].

Prior to Maraviroc administration, it is mandatory to identify the viral tropism. Various phenotypic and genotypic methods have been developed. The need to the test patients prior to treatment may limit the use of maraviroc and could represent an impediment for the clinicians who need a quick regimen change[14].

The aim of this study is to assess which indications led to the execution of the test for viral tropism and the percentage of treated patients compared to tested individuals. Moreover, we evaluated the efficacy and tolerability of MVC based regimens in a group of multi-experienced patients in a Sicilian multicenter cohort of HIV-1-infected individuals.

MATERIALS AND METHODS

An observational retrospective multicenter study was performed in 15 centers for diagnosis and treatment of AIDS in Sicily. The study is expected to enroll all patients who underwent to the Trofile™ or the genotype test to determine the CCR5 viral tropism.

Clinical records of 213 HIV+ subjects screened for viral tropism were reviewed for the following variables: epidemiological (sex, age, modes of HIV acquisition), clinical (clinical stage of the patients tested according to CDC classification, HIV RNA Viral Load, CD4 count, number of regimens), indications for the test (virological and/or immunological failure, toxicity, intolerance, proactive switch, naive patients, screening, therapeutic simplification), test execution (time to test response, implementing rules, test results - R5, D/M, X4, not determined - proposed treatment - yes or no).

Within subjects treated with MVC, start date of MVC therapy, time elapsed between the date of execution of the test and the initiation of therapy, new therapeutic combination; monitoring of the virological and immunological efficacy parameters (HIV RNA viral load (VL) and CD4 T-cell counts and metabolic parameters trend measured at time 0, and then every 4 months until 24th); treatment outcome (responders, non-responders or failure, rebounder, interruption); adverse events recorded; any reasons for suspension and/or interruption of the treatment.

Absolute frequency and percentage have been used for categorical variables. The descriptive statistical analysis was performed using the mean, standard deviation, minimum and maximum for parametric data and the median and interquartile range (IQR) for non-parametric data. For the comparison of categorical variables it was used X2 test with Yates correction and the Fisher exact test. As treated (AT) analysis and Intention to treat (ITT) analysis were applied to evaluation of virological efficacy.

RESULTS

Overall, data regarding 213 tests for the tropism were evaluated. Efigurepidemiological data on tested patients are reported in Table 1.

39.3% subjects had a previous diagnosis of AIDS (CDC C). The median HIV RNA viral load was 28134 (IQR 1712-130,375) copies/ml; 25.4% subjects had an HIV RNA viremia more than 100,000 copies/ml. At the same time, the median CD4 T-cell count was 217 (IQR 122-370) cells/µl. Median number of antiretroviral regimen used was 4 (IQR 2-7).

Table I. Epidemiological aspects of 213 subjects screened for viral tropism.

Males		143 (67.1%)
Females		70 (32.9%)
Median age (IQR) years		44 (40-50)
Routes of infection:	Drug users	46 (21.6%)
	MSMs, bisexuals	60 (28.2%)
	Heterosexuals	93 (43.7%)
	Others	14 (6.5%)

At the time of test 200 (93.8%) subjects were on therapy. 13 (6.2%) patients were naive or had just interrupted treatment for different reasons. Data about various therapeutic regimen used are showed in Figure 1.

110 (51.6%) patients had a resistance test before performing the tropism test. 10 (4.7%) patients showed a wild type profile. In other cases there were protease (2%) or transcriptase (5%) mutations or both (37%). 103 (48.4%) resistance tests were not performed, sometimes because of plasma viremia below the sensitivity level of the resistance test used.

Indications to viral tropism test more frequently reported were virologic and/or immunologic failure in 155 (72.7%) cases; 12 (5.6%) were analysed for intolerance/toxicity to the previous regimen. 166 (77.9%) subjects were screened with Trofile test. The test results turnaround time was within a median of 20 (IQR 15-30) days independently from the used methods.

In 121 (56.8%) cases an R5 tropic virus was detected, a dual tropic virus (D/M) was found in 46 patients (21.6%), in 15 cases (7.0%) an X4 virus was present, in 31 (14.5%) the samples could not be performed or sequenced. Data regarding the different response to the test and motivation for performing it are reported in Figure 2

We did not find any difference between the two viral tropism tests methods used (p = 0:31), although a reduced number of indeterminate tests was observed with the genotypic test (2.7% *vs.* 15.9%). There wasn't a different distribution of viral tropism based on gender (p = 0.89) or according to the CDC clinical stage. Data relating to the CDC clinical stage and the test result are reported in the Figure 3.

Data relating the CD4 category (respectively >200 and ≤ 200 cells/µl) and plasma viremia recorded at baseline and the viral tropism are respectively shown in the Figures 4 and 5.

Finally, it was researched whether the different viral tropisms could be attributed to a greater or lesser exposure to ARVs (prior therapeutic lines) as a surrogate for duration of infection and/or previous treatment failures. Data relating to therapeutic lines at the time of test run are shown in the Figure 6.

A total of 76 subjects started ART. 45 (59.2%) underwent to the resistance test and 3 had a wild type profile. A total of 72 (95%) resulted R5 tropic and 4 (5%) D/M. No one with an X4 result was initiated to treatment with Maraviroc. The median time between the date of the test and start of treatment with MVC was 82 (IQR 45-116) days.

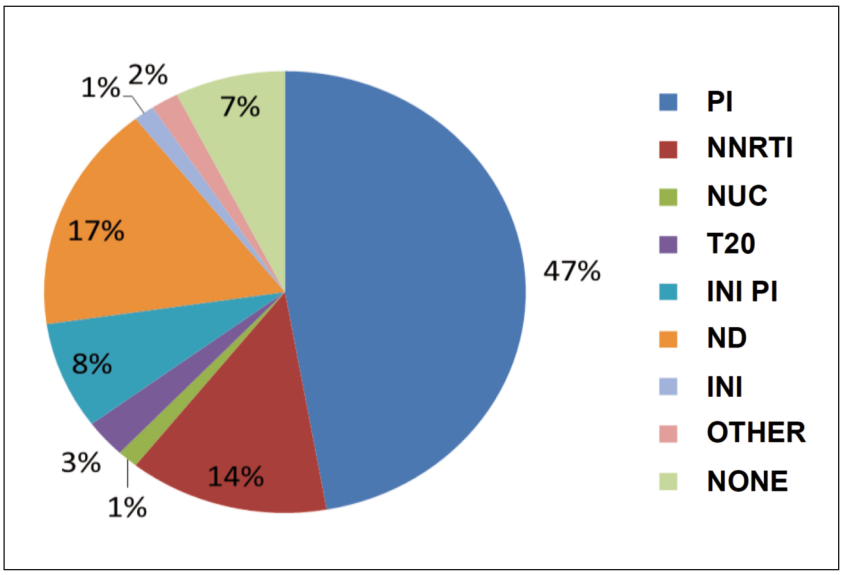
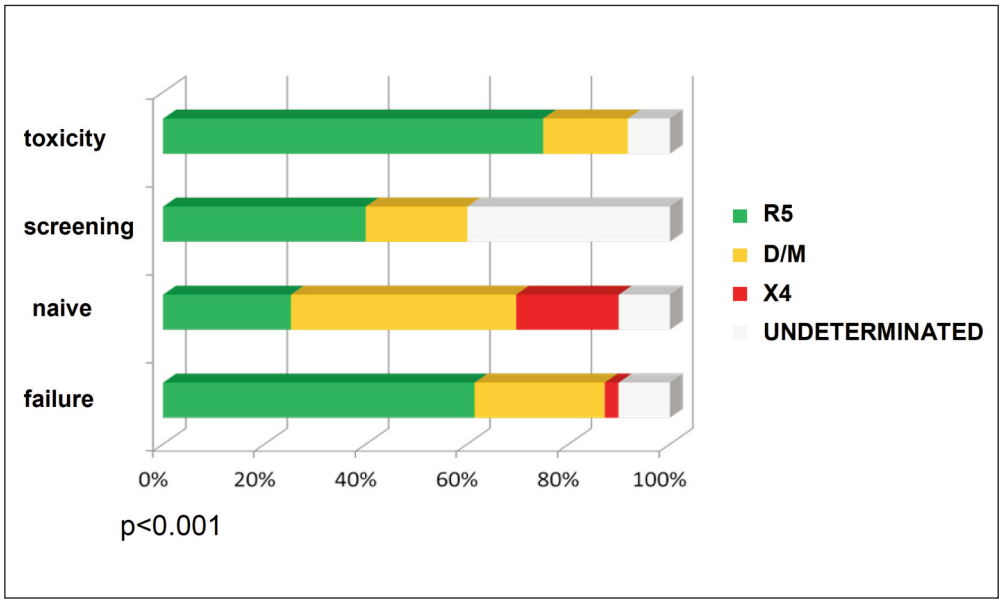


Figure 1. Antiretroviral treatment at time of tropism test.

Figure 2. Motivation for tropism test and response.



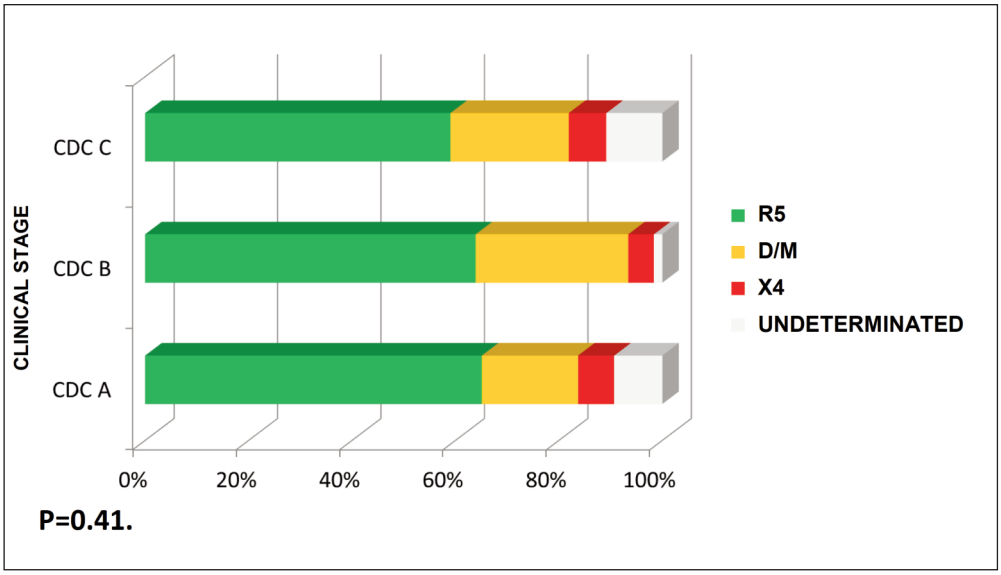


Figure 3. CDC clinical stage and viral tropism.

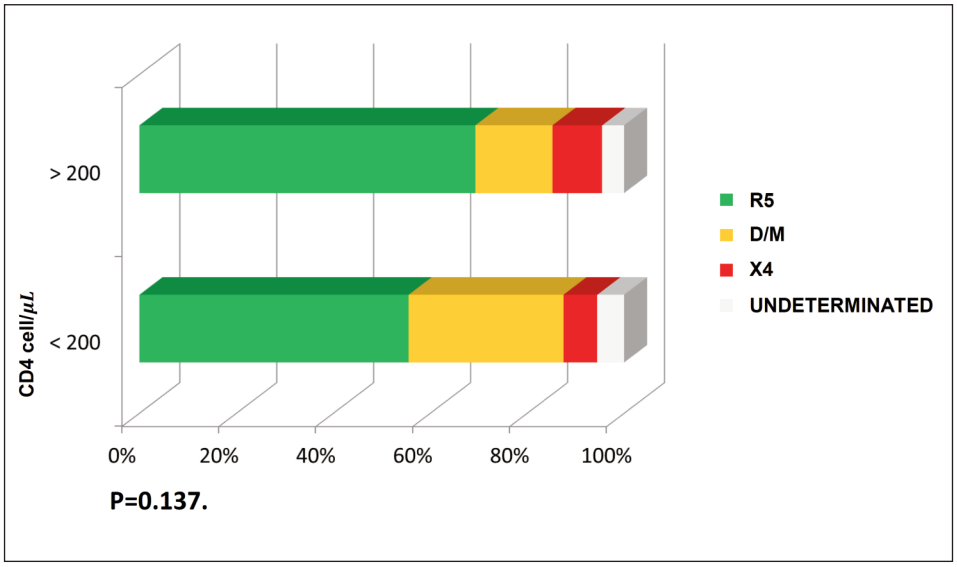


Figure 4. CD4 cell count and viral tropism.

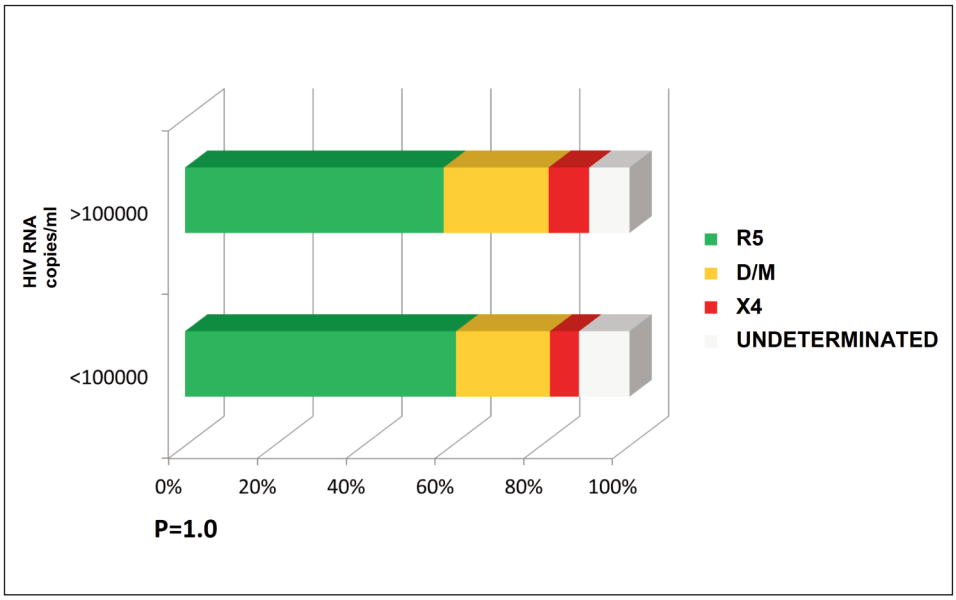


Figure 5. Levels of plasma viremia HIV RNA and viral tropism.

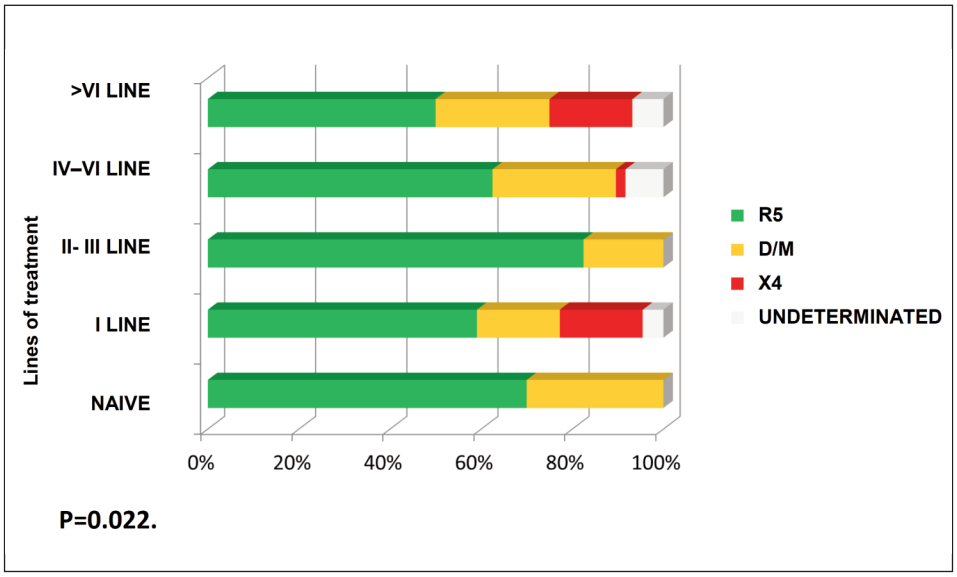


Figure 6. Number of previous ARV therapeutic lines and viral tropism.

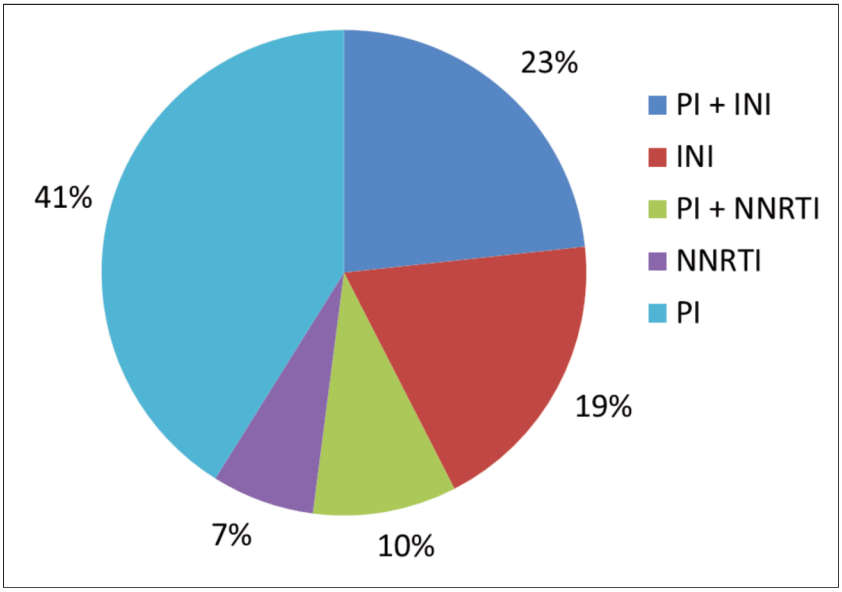


Figure 7. New combination therapies used in patients treated with MVC.

Regarding the new combination therapies used in association with MVC, 54 (71%) patients used a PI based combination, 17 (31.5%) of these in association with RAL; 14 used an INI (integrase inhibitor) based combination, 5 a NNRTI one, 3 a NRTIs therapy. Data relating the different combination therapies used are shown in the Figures 7, 8 and 9.

The analysis on efficacy of the treatment has shown that after 12 months of a MVC based regimen 56.8% (ITT analysis) and 61.7% (AT analysis) of patients had HIV RNA<50 copies/ml; median CD4 cell count was 387 (IQR 222-455) cells/ml. After 24 months 64.8% (ITT analysis) and 80% (AT analysis) had HIV-RNA below 50 copies/ml. Median CD4 cell count was 381 (IQR 218.515) cells/ml with a median increase of 168 (IQR 54-274) cells/ml. Data relating the CD4 count trend in patients treated with MVC are shown in Figure 10. Finally, at 24 months the median value of total and HDL cholesterol and triglycerides were within the normal range.

Two cases of rush and one of headache have been reported. In one case it was necessary to stop treatment for toxic effects. Overall seven therapy interruptions were registered: in two cases for the death of the patients; in one case for adverse reaction; in four cases for treatment failures, three of which due to poor compliance and low adherence.

CONCLUSIONS

Maraviroc is the first CCR5 inhibitors approved for HIV-infected patients harboring R5-tropic viruses; although the drug showed a good safety profile, its use in clinical practice has been limited to the treatment of antiretroviral-experienced patients failing prior regimens, most of them for salvage treatment[15-22]. Some limitations to larger use could be related to the high cost and the mandatory tropism test to be performed before prescription. Also, in our region difficulties related to the access to the test

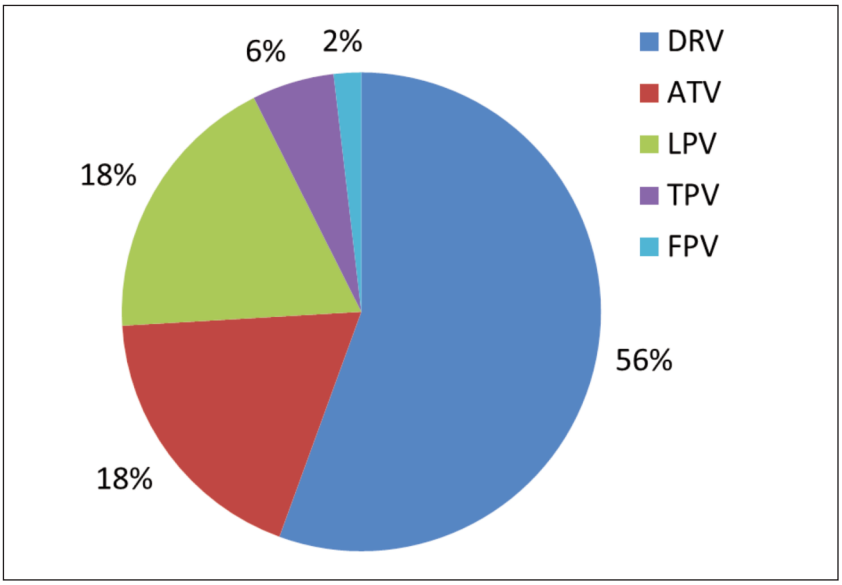


Figure 8. Proteases Inhibitors used in patients treated with MVC.

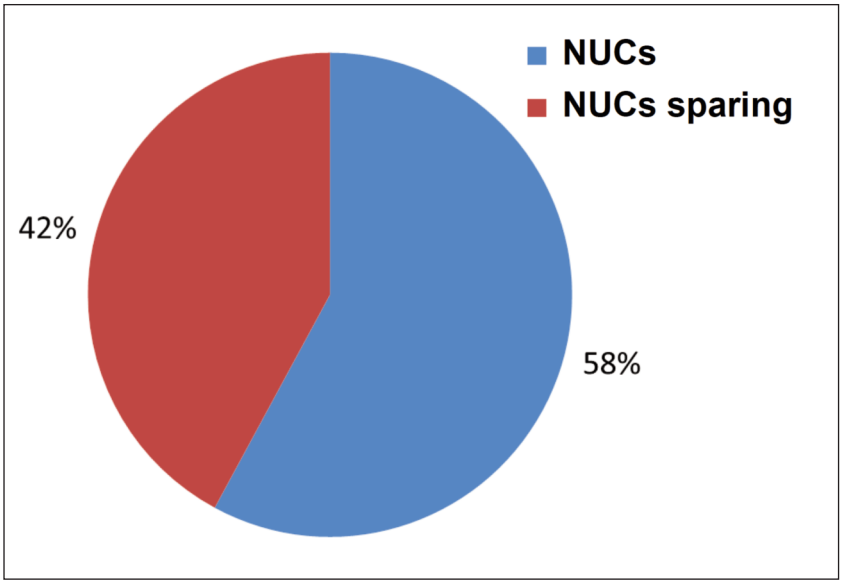


Figure 9. NUCs sparing therapeutic regimen in patients treated with MVC.

could have limited the use of this drug. This study represents one of the first attempts to collect retrospective data on patients treated with antiretroviral drugs in Sicily.

Overall, we evaluated data related to 213 tests for the tropism. As expected, regarding the clinical stage of the subjects who underwent viral tropism test, the number of symptomatic patients with a previous diagnosis of AIDS (CDC C) was high (around 40%), while the largest number of tests has been proposed to patients with plasma viremia less than 100000 copies/ml. The CD4 count median at the time of test was low with a growing trend during the time; similar results were found in the sample analyzed by Dentone et al[9].

Half of the patients tested came from a PI-based regimen and only a minority were using raltegravir. This could be due to the time when the analysis was performed; in fact, the use of integrase inhibitors was limited for high cost. On the other hand, been integrase inhibitor unexperienced gave the physician the possibility to use it in combination therapy with maraviroc, hence, having more drugs in the armamentarium.

Only half of patients received, prior to or simultaneously with the test for tropism, a test for the evaluation of viral resistances. This may represent a limitation in selecting the therapy to be associated with MVC.

The main reason behind the execution of the test for the tropism was treatment failure (71.7%). Most of the tests were performed using the Trofile test. Despite, at that time, the genotypic method did not require sending samples abroad, and is considered more rapid and simple, the time needed to get the results still appeared completely similar to the Trofile assay[11].

Almost half of subjects had an R5 virus. The two tests performed equally.

The reasons for which more than a third of the subjects with R5 tropism were not specifically treated were

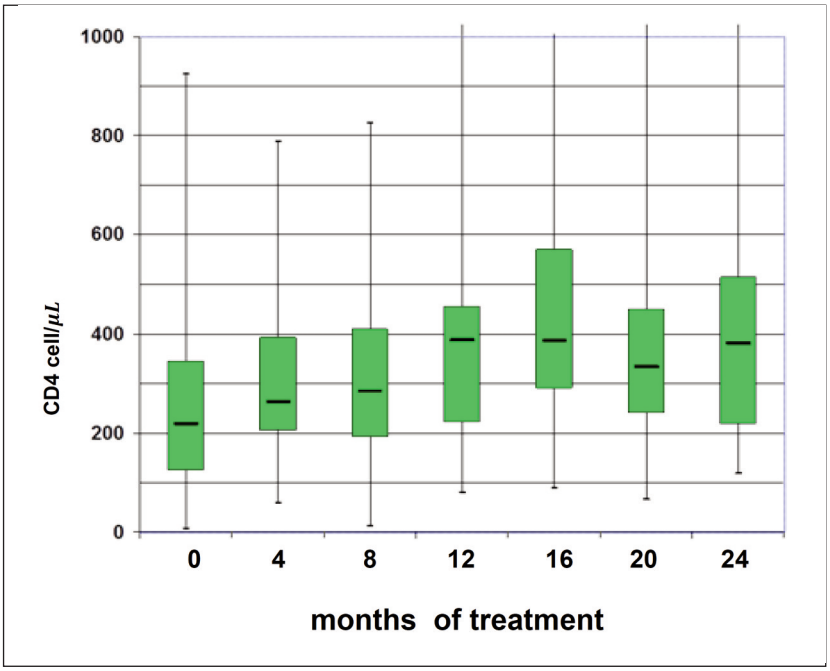


Figure 10. CD4 cell count in patients treated with MVC based regimens.

not investigated, but may reside in the fact that in a number of cases, the test was carried out for screening or in naive subjects and not for a therapeutic switch. It is also possible that in some cases the late arrival of results has caused different treatment choices.

Therapy with MVC was undertaken after a median of 82 days from the time of testing.

Over two-thirds of the patients were treated with a new combination with MVC associated with a PI; a third of these patients also used raltegravir. It seems evident that in the new combination, drugs with high genetic barrier have been privileged, in particular darunavir.

The efficacy analysis shows a progressive increase in CD4 and a progressive increase of patients with undetectable viral load.

The treatment with MVC was well tolerated. These data, however, seem to confirm the findings from the pivotal clinical and observational cohort studies[8-9,15-16].

In conclusion, the data from this retrospective study seems to confirm what the literature has so far produced. The new genotypic test has added additional sensitivity and specificity to the test.

The addition of MVC to an optimized therapeutic regimen, better if coupled with the resistance profile, has enabled the control of viral replication and an adequate immune reconstitution in a significant number of multi-experienced patients. MVC stands in the landscape of drugs and in the rescue strategy, both in the early failures for switch or toxicity, and it appears a safe and well-tolerated treatment.

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

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