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THERAPEUTIC STRATEGIES IN HIV INFECTED PATIENTS IN TREATMENT FAILURE

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Abstract. Objectives: Analisys of clinical course after changing antiretroviral therapy (ART) in HIV infected patients (Px) with treatment failure (TF). **Methods:** A retrospective study in Craiova Regional Center for Monitoring and Evaluation of HIV/AIDS from 01/01/2009 to 12/31/2009, on two groups of Px in TF with at least 3 previous ARV scheme, Px in whom a new ART scheme was introduced: group A (16 Px) according to resistance test results and previous ART schemes and group B (23 Px) depending on previous ART schemes. **Results:** Clinical and immunological CDC staging- group A versus B was similar : B2 stage 1 Px (6.25%)/1 Px (4.34%), B3 stage 9 Px (56.25%)/7 Px (30.43%), C2 stage 1 Px (6.25%)/2 Px (8.69%), C3 stage 5 Px (31.25%)/13 Px (56.25%), median CD4=104 vs 181 cells/mm^3, median HIV-RNA=4.49 vs 4.30 lg copies/ml. Darunavir (DRV), Etravirine (ETV), Raltegravir (RAL) were included in ART of 8 Px (50%) of group A vs. 9 Px (39.14%) in group B. Clinical outcome was good in 14 Px in group A and all Px in group B. In group A, 1 Px died with lymphoma and 1 Px had cerebral toxoplasmosis. HIV-RNA level, at 4 and 12 month, in group A vs group B, were: HIV-RNA <50 copii/ml- 13 Px (81.25%) vs 18 Px (78.26%) (p> 0.05; 0.19 <OR = 1.20 <7.91; CI 95%), respectively, 14 Px (93%) vs 20 Px (86.95%) - (p> 0.05; 0.12 <OR =1.05 <10.57; CI 95%). Median CD4 (cells/mm ^{3}) was: 253 vs. 314, respectively 393 vs. 344. Increases in CD4 levels was recorded in: group A at 13 Px (81.25%) vs. 17 Px (73.91%) in group B (p> 0.05; 0.26 <OR = 1.53 <9.68). All Px with DRV, ETV, or RAL had HIV-RNA <50 copies/ml and increasing CD4 value at 4 and 12 months. **Conclusions:** 1. Using DRV, ETV and RAL in HIV infected Px with TF was associated with favorable outcome independent of resistance testing, which is important in limited financial resources settings. 2. Control of viral replication and immunological success, unrelated to the immunodepression at the time of TF were similar in both groups. 3. Group size and duration of the study are relatively small and do not allow definitive conclusions, but the results urges for further monitoring.
Keywords: HIV, ARV, Resistance

Introduction

TF may limit ART options. In such Px with limited options is indicated by some authors to continue the original ART, even if partial viral suppression is achieved. On the other hand, incompletely suppressed HIV shows high rates of replication and mutation.

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ART objective is to obtain a maximum suppression of HIV replication. Major risk factors for virological failure are: development of resistance, previous antiretroviral therapy and and poor adherence to treatment [1].

Resistance testing before starting antiretroviral therapy as recommended by international guidelines, is accompanied by high rates of therapeutic success. This situation becomes problematic when such tests are unavailable, as in countries with limited financial resources, especially in multiexperienced Px or TF, in which choosing individual, optimal combination has major importance for

Px outcome and also preserves future options for succesfull treatment.

The introduction of new ARV: DRV, ETV, MVC, RAL, will facilitate obtaining a rapid viral suppression, „key" to success are judicious use of them.

The objectives of this study were to analyse clinical and biological evolution after changing ART in HIV infected Px with TF, with/ without antiretroviral resistance testing.

Material and methods

Retrospective study conducted in Craiova Regional Center for Monitoring and Evaluation of HIV / AIDS from 01/01/2009 to 12/31/2009 on two groups of Px in TF, with at least 3 previous ARV schemes, in whom a new ARV scheme was introduced: in group A (16 Px), according to resistance test results and previous ART and group B (23 Px) depending on previously used ARVs.

In both groups, we included only those Px with good adherence to ARV therapy and those in which no major adverse reactions were observed.

We monitored: the evolution to AIDS and decease, immunological and virological dynamics in 12 months after therapy switch. The follow up included: clinical outcome measured by AIDS defining illness or death, changes in HIV RNA and CD4 levels). For each batch was analyzed the immunity level after the introduction of new ARV scheme. Statistical analysis was performed using EpiInfo program by calculating the threshold (p) of statistical significance and odds ratio (OR); p values <0.05 and OR> 2 were considered statistically significant.

Results

Demographics dates was: in group A, median age = 20 years, sex ratio: 9 F/7M (56.25%, 43.75%), in group B, median age = 21 years, sex ratio: 17 F/6 M (73.91%, 26.09%).

At TF time, clinical and immunological staging was as follows, in group A: 1 Px (6.25%) - B2, 9 Px (56.25%) - B3, 1 Px (6.25%) - C2, 5 Px (31.25%) - C3, median CD4 = 104 cells/mm ^{3}, median HIV-RNA = 4.49 lg copies/ml; in group B: 1 Px (4.34%) - B2, 7 Px (30 , 43%) - B3, 2 Px (8.69%) - C2, 13 Px (56.52%) - C3, median CD4 = 181 cells/mm ^{3}, median HIV- RNA = 4.30 lg copies/ml.

The number of ARV regimes used before the introduction of new ARV regime, at TF moments, was as follows: in group A, 6 Px (37.5%) with 3 ARV regimes, 7 Px (43.75%) with 4 ARV regimes and 3 Px with 5 ARV regimes and in group B: 19 Px with 3 ARV regimes and 4 Px with 4 ARV regimes.

In group A, the resistance test results revealed the following mutations: for NRTIs: M41L-3 Px (18.75%), D67 N-8 Px (50%), T69 D-8 Px(50%), V57 T-5 Px(31.25%),

V118 I-5 Px (31.25%), L210 W-3Px (18.75%), T 215 Y, F,C,S-9 Px (56. 25%), K 219

R,E,Q-8Px (50%), K70 R-5 Px (31.25%), L 74 I-V-5Px (31.25%), M184 V-14 Px (87.5%); for NNRTIs: L100 I- 3 Px (18.75%), K103 N- 11 Px (68.75%), M230 L- 3 Px (18.75%) and for PIs: L10V- 15 Px (93.75%), G 48 V- 8 Px (50%), I 50 V- 5 Px (31.25%), I54

S-V-11 Px (68.75%), V82 A-12 Px (75%), M36 I-7 Px (43.75%), K 20 R- 7 Px

(43.75%), K 43 T-8 Px (50%), M 46 I-5 Px (31.25%) , L24 I-3 Px (18.75%), V77I-5

Px (31.25%), L 33 F-3 Px (18.75%), A 71V-3 Px (18.75%), L 90 M-3 Px (18.75%)

Newly introduced ARV scheme: in group A- NRTIs + PI/r (non-DRV)- 6 Px (37.5%), 2 NRTIs + DRV / r + FI + II-2 Px (12.5%), NRTIs + DRV / r + II-2 Px (12.5%), NRTIs + FI + DRV/r-1 Px (6.25%), NRTIs + FI-1 Px (6.25%), FI + DRV / r + II-1 Px (6.25%), NRTIs + DRV/r- 1 Px (6.25%), NRTIs + DRV / r + ETV-2 Px (12.5%), in group B- NRTIs + FI-4 Px (17.39%), NRTIs + PI/r (non-DRV)- 10 Px (43.47%), NRTIs + DRV / r - 4 Px (17.39%), NRTIs + DRV / r + ETV-3 Px (13.04%), FI + II + DRV/r-1 Px (4.34%), NRTIs + DRV / r + II -1 Px (4.34%).

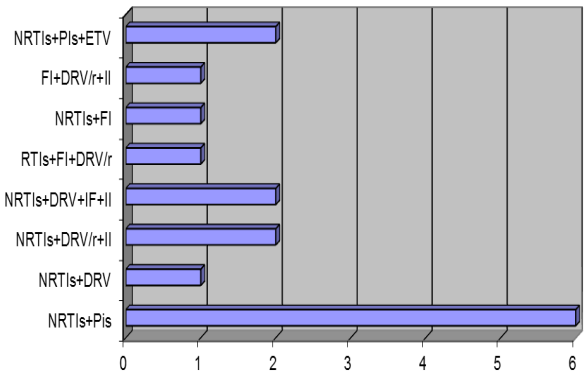

Figure 1. Number of studied patients on different ARV schemes for group A

DRV, ETV or RAL were used in ARV scheme in 8 Px (50%) of group A vs. 9 Px (39.14%) of group B.

The clinical course was favorable in 14 Px in group A, 1 Px was diagnosed with lymphoma in march 2009 and died eight months after changing ART and 1 Px developed cerebral toxoplasmosis four months after changing ART; in group B, favourable evolution for all Px .

In group A, HIV-RNA level, at 4 and respectively 12 months after changing ART were: 13 Px

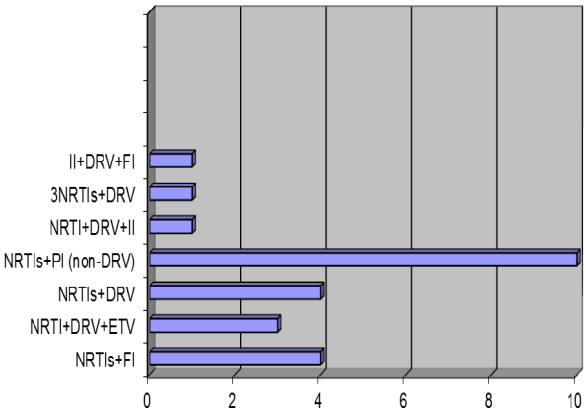

Figure 2. Number of studied patients on different ARV schemes in group B

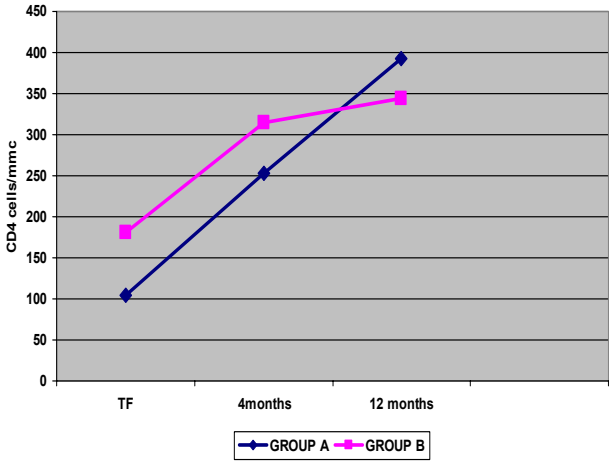

Figure 3. Median CD4 trend in group A vs group B

(81.25%) respectively 14 Px (93%) had HIV- RNA <50 copies/ml. Median CD4 count was 253 cells/ mm^3 at 4 month, respectively 393 cells / mm^3 at 12 month.

In group B, HIV-RNA level, after 4 and respectively 12 months of ART change follow up: 18 Px (78.26%) and 20 Px (86.95%). Median CD4 count was 314 cells/mm^3 at 4 month, that the 344 cells/ mm^3at 12 month.

Comparing control of viral replication between the two groups we found that there was no statistical significant difference after 4 months (p> 0.05, 0.19 <OR = 1.20 <7.91; CI 95%) and 12 months (p > 0.05, 0.12 <RR = 1.05 <10.57; CI 95%) of treatment. (Table I, Fig. 3, 4)

Viro-immunological discordant values were found in 2 Px (12.5%) of group A vs 3 Px of group B (13.04%).

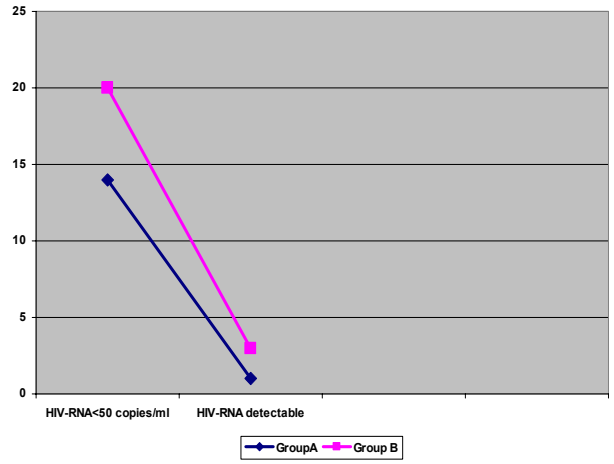

Figure 4. HIV-RNA level trends in group A vs group B at 12 month

	4 months		12 months	
GROUP	CD4 median (cells/mm^3)	VL <50 copies/ml (nr.Px;%)	CD4 median (cells/mm^3)	VL <50 copies/ml
A	253	13 (81.25)	393	14 (87.5)
B	314	18 (78.26)	344	20 (86.95)

Table I. Viro - immunologic issues at 4, respectively 12 months after changing ART

Clinical failure was asociated in studied Px with detectable levels of HIV- RNA and no increase in CD4 levels after 4 month of treatment with a new combination ARV: NRTIs+PI/r (non-DRV).

In group A we found increased CD4 value in 13 Px (81.25%) vs 17 Px (73.91%) in group B (p> 0.05, 0.26 <RR = 1.53 <9.68; CI 95%) (Table II).

Improved CD4 levels and undetectable HIV-RNA were found in group A Px with the following ARV schemes: PI/r (non-DRV)+ NRTIs- 1 Px,

Group	Increasing CD4 number	p
A	13 Px (81.25%)	p>0.05
B	17 Px (73.91%)	

Table II. Immunological evolution in group A vs group B

NRTIs+PI/r (non-DRV)- 4 Px, to Px in group B, with: NRTIs +FI-1 Px, NRTIs+PI/r(non-DRV)- 7 Px, 3 NRTIs+PI/r (non-DRV)- 1 Px, and in all Px with DRV, RAL or ETV, in various combinations in both groups.

All Px treated with new therapeutic agents: DRV, ETV or RAL had HIV-RNA <50 copies/ml and increased number of CD4 lymphocytes at 4 and 12 months of new ARV treatment regimes. Median CD4 = 420 cells/mm^3 to 4 months and median CD4 = 483 cells/mm^3 to 12 months vs. baseline median CD4 = 104 cells/mm^3.

Discussion

The clinical success of ART is correlated with viro-immunological dynamics and quantified in most studies by evolution to AIDS stage and death [2,3,4], also confirmed in our study. Px which showed clinical failure have also viro-immunological failure.

Prospective studies [5,6] have demonstrated the importance of resistance tests before changing ART, showing the necessity and effectiveness for classes of NRTIs, NNRTIs, PIs, but the clinical relevance of using II or CCR5 antagonists has not been proven yet in clinical studies [7]. DRV, ETV, RAL or MVC had remarkable effects even in the presence of multiple resistance mutations [8,9].

In this study, the Px who had successful immunologic change after ART, CD4 lymphocytes showed a rapid increase in first 4 months, followed by a slow ascendent trend quantified by the second measurement of CD4 lymphocytes to 12 months, according to other studies [2,10,11], also observed in both group A and B, as well as Px which had received DRV, ETV, RAL.

Immunological success after ART did not correlate with the number of CD4 lymphocytes at the time of TF, discordant with data from literature [12].

Gaining control of viral replication in all Px with DRV, ETV or RAL, based on resistance test results and history of ARVT or just on the history, justifies the role of the latter in scheme selection to Px in TF, in situations of limited financial resources when the resistance test is not available and the use of new therapeutic agents is needed.

The study is limited and accompanied by risks of bias, due to several factors: the small number of Px in both groups, the relatively short period of study, and lack of HIV-RNA determinations in all Px in both groups at 4 and 12 months introduction of new ARV regimes. Also, the percentage distribution of different use of new ARV therapeutic agents (DRV, RAL, ETV) between the two groups does not allow a reliable comparison between them.

In the future, it would be interesting to compare the evolution of the Px with TF who received ARV regime which included only new therapeutic agents (DRV + RAL + ETV) with other ARV scheme.

The lack of more resistance testing in Px with a history of at least three ARV scheme does not allow to point all present mutations that could alter the study results. The impact of new therapeutics agents on clinical and biological evolution of Px with HIV infection, even without resistance test, remains a goal of interest.

Conclusions

Using DRV, ETV or RAL in HIV infected Px with TF was associated with favorable outcome independent of resistance testing, which is important in limited financial resources.

Control of viral replication and immunological success, unrelated to the immunodepression at the time of TF were similar in both groups.

Relatively small group size and duration of the study do not allow definitive conclusions, but the results urges for further monitoring.

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