Discordant response to highly active antiretroviral therapy in Mexican pediatric patients infected with HIV/AIDS

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Abstract

Background: The goal of antiretroviral (ART) therapy is to control human immunodeficiency virus replication and to increase CD4 T-cell count. Discordant response to ART occurs when only one of these two objectives is achieved.

Methods: Pediatric patients who attended the Clínica de Inmunodeficiencia at Hospital Infantil de Mexico Federico Gomez were studied retrospectively. Response to a PI-based highly active antiretroviral therapy (HAART) was classified as optimal, failure, discordant response with viral failure and discordant response with viral success. Demographic data, viral load and CD4 T-cell count (baseline, 6-month and 12-month follow-up determinations) were analyzed.

Results: Fifty six patients were included. Mean age of patients was 30.5 months. Discordant response was seen in 45% and 53.5% at 6- and 12-months follow-up, respectively.

Conclusions: Discordant response was seen in >50% of our study population and is a common scenario; clinical implications are still unknown. Discordant response should not be interpreted, especially during the first 12 months of therapy, as a failure of HAART.

Key words: human immunodeficiency virus, pediatrics, infection, acquired immunodeficiency syndrome, antiretroviral treatment, discordant response.

Introduction

The use of highly active antiretroviral therapy (HAART) has improved the survival of patients infected with human immunodeficiency virus (HIV), slowing the progression of the infection towards acquired immunodeficiency syndrome (AIDS). This is achieved through an immunological recovery with increase of CD4 T-cell count and decrease in viral load to undetectable levels.1,2

Viral load and CD4 T-cell counts are the most commonly used parameters to monitor the efficiency of antiretroviral treatment.3

Because of the association observed between immunologic and virologic responses in the first months of treatment, it has become a common practice to follow-up these parameters to determine therapeutic success or failure and evaluate changes in antiretroviral treatment in early stages.4-7

There are groups of patients where viral replication is suppressed appropriately but without immunologic recovery (virologic success/immunologic failure [VS/IF]). On the other hand, there are patients with immunologic recovery but without an important decrease in viral load (virologic failure/immunologic success [VF/IS]). These two scenarios are known as discordant responses.8-12
In studies carried out in adults, discordant responses have been observed in up to 20% of cases with HAART. Most of these studies describe an association between discordant response and a higher risk for developing AIDS. This would define discordant response as a poor prognosis factor and a sign to change antiretroviral treatment.13-20

It has been observed that discordant responses are more frequent in the pediatric population than in adults. However, there are differences in the immunologic system and HIV behavior in children that do not allow extrapolation of results from adult-population studies. 14,17,21-23

There are few studies about clinical and therapeutic implications of discordant response to HAART. Most studies do not include the pediatric population and have methodological limitations that do not allow for the comparison of results.

This study analyzes the frequency and characteristics of patients with discordant responses to treatment as well as of patients with optimal or failure response to HAART with protease inhibitor (PI).

Patients and Methods
We carried out a descriptive and retrospective study including patients with HIV infection <18 years old who attend the Immunodeficiency/HIV Clinic (CLINDI) of Hospital Infantil de Mexico Federico Gomez. The clinic offers medical care to ~200 HIV-infected pediatric patients.

Inclusion criteria were 1) patients <18 years old with HIV infection, 2) patients who received PI-based HAART as their first-line treatment, 3) patients with viral load and CD4 T-cell counts for baseline, 6-month and 12-month follow-up with complete clinical files.

We excluded patients who changed from PI-based HAART to a different treatment or patients without complete 12-month follow-up or those who lacked a complete clinical file.

HAART Response
We classified immunologic/virologic response into four groups:

a) Optimal with VS/IS: CD4 T-cell count increase that allows the classification of a patient to a lower immunosuppression level (according to CDC classification) and undetectable viral load (defined as <400 copies/mL in order to compare our results with other studies)

b) Failure with VF/IF: CD4 T-cell count remains at previous levels or reaches a higher immunosuppression level (CDC classification) and viral load >400 copies/mL

c) Discordant with VS/IF: CD4 T-cell count remains at previous levels or reached a higher immunosuppression level (CDC classification) and undetectable viral load

d) Discordant with VF/IS: CD4 T-cell count increase with improvement in immunosuppression level (CDC classification) and viral count >400 copies/mL

To define immunosuppression level, we used the percentage of CD4 T-cells in patients <5 years of age and total CD4 T-cell count in patients >5 years of age, according to the recommendations of the National Institutes of Health (U.S.).

We analyzed demographic data, viral load and CD4 T-cell count (baseline, 6-month and 12-month follow-up determinations).

Results
We included 56 patients who fulfilled selection criteria.

![Figure 1. Overall virologic and immunologic behavior at 6 and 12 months after HAART in 56 pediatric HIV patients at Hospital Infantil de Mexico Federico Gomez. Changes in CD4 T-cell counts and viral load in studied population at 6 and 12 months follow-up (n = 56).](image)

Average age at admission was 30.5 months (range: 2-113 months). Of these patients, 29 (52%) were <2 years of age, 20 (36%) were between 2 and 5 years of age, and 7 (12%) were >5 years of age.

We found no significant difference in gender distribution among patients: 30 were female and 26 were male.
Average viral load was 391,015 copies/mL (5.59 log10) at admission, 89,705 copies/mL (4.95 log10) 6 months after beginning HAART and 85,299 copies/mL (4.93 log10) 12 months after beginning HAART.

The average CD4 T-cell count was 767 cells/mL (18%) at admission, 1064 cells/mL (21%) 6 months after beginning HAART and 1177 cells/mL (24%) 12 months after beginning HAART (Figure 1).

**Group Analysis According to Treatment Response**

Table 1 shows characteristics of groups according to HAART response.

The group with optimal response (VS/IS) presented a reduction in viral load from 5.61 to 2.09 log10 copies/mL during the first 6 months of treatment and reached 1.93 log10 copies/mL after 12 months of treatment. This group remained with immunosuppression definition levels (16% CD4 T-cells) and remained without immunosuppression after 6 and 12 months of treatment (26.7% and 29.5% average CD4 T-cells, respectively).

In the group with treatment failure (VF/IF), patients maintained similar viral loads to baseline (5.57 log10 copies/mL baseline, 5.56 log10 copies/mL after 12 months of HAART treatment).

In cases with discordant response, we identified 25 patients...
Figure 2. (a-d) Behavior of four different response groups at 6 and 12 months of HAART in 56 pediatric HIV patients at Hospital Infantil de México Federico Gómez. Changes in CD4 T-cell counts and viral load (log10) by HAART response group at 6 and 12 months follow-up.

(45%) after 6 months of treatment: 19 (34%) presented VF/IS and six showed VS/IF. After 12 months of treatment, 30 patients (53.5%) presented discordant response: 17 (30.4%) had VF/IS and 13 (23.2%) showed VS/IF (Figures 2a-2d).

Table 2 shows response group changes during the study; 40% of patients with optimal HAART response remained in the same category 6 months after treatment. Only one patient was classified as therapeutic failure at 12 months and 50% of patients switched to a discordant response group (five as VS/IF, three as VF/IS).

Of 16 patients with therapeutic failure at 6 months, five patients (31%) switched to optimal response at 12 months, two patients (12.5%) remained as therapeutic failure and 9 (56%) showed discordant response at 12 months.

In general, patients with discordant response at 6 months after beginning HAART showed a trend to remain in the same group; however, four patients with VF/IS switched to therapeutic failure 6 months after beginning treatment.

It was not possible to identify significant associations between immunologic or viral characteristics before beginning HAART and the results after 6 and 12 months of treatment.

Discordant response was not associated with a higher number of infections or death during the reference period (data not shown).

Discussion
Currently, HAART is the most important treatment for management of HIV patients.

It is not possible to guarantee the success of standard treatment in all patients because of host characteristics (coreceptor mutations or mutations in therapeutic antiretroviral targets) or because of virus characteristics (mutations associated with resistance to different types of
antiretrovirals).\textsuperscript{4,12,23,24}

Developed countries began to analyze HIV genotypes searching for mutations associated with antiretroviral resistance in patients who presented treatment failure. This practice is expanding to patients without previous treatment, with the purpose of providing “customized” treatment from the beginning and reduce the risk of therapeutic failure.\textsuperscript{25,26}

However, most HIV patients reside in developing countries where there are limited conditions to carry out genotype studies and there are few antiretroviral options.

In developing countries, clinical evolution, viral load and CD4 T-cell count follow-up are the only tools available to physicians for evaluation of treatment efficiency.\textsuperscript{4,27}

As for the pediatric population infected with HIV, discordant responses have been reported in up to 50% of cases, especially during the first months of HAART.\textsuperscript{14,28} Because prognosis implications are unknown after discordant response, it can be interpreted as therapeutic failure and lead to change of antiretroviral treatment, which implies higher medication toxicity, difficult to manage treatments with less adherence, and depletion of limited resources.

This is the first report about the frequency of discordant responses in HIV-infected Mexican children who received PI-based HAART as their first-line treatment.

The frequency of discordant response after 6 months and 12 months of treatment was 45% and 53.5%, respectively. These findings agree with previous studies carried out in children reporting that discordant response is much more frequent in the pediatric population than in adults.\textsuperscript{8,22}

Nicastri et al.\textsuperscript{7} carried out a study with >2100 adult patients and an average 44-month follow-up. They found that patients with discordant responses had a lower risk for developing AIDS than patients with therapeutic failure; however, they presented twice the risk of dying or developing new HIV-related events than patients with optimal response.

Ghaffari et al.\textsuperscript{8} analyzed virologic and immunologic responses during 96 weeks in 40 pediatric patients who received PI-based HAART. They found virological failure in 57.5% of cases 6 months after beginning HAART, without having a discordant response (VF/IS) associated with poor clinical evolution or negatively impacting patient’s height and weight when compared with the optimal response group.

Our study has several limitations. First, the studied sample is not very large and this compromises statistical power to determine risk factors. Second, we chose a cut-off point where VS was <400 copies/mL in order to be able to compare our results with previous studies, even though current techniques allow defining undetectable viral load as <50 copies/mL. Previous studies defined IS as an increase in CD4 T-cell count. Our group defined this as a positive change in immunosuppression level classification according to CDC because this classification has a greater impact on clinical prognosis for HIV patients. Also, because we lack a long-term follow-up, it is not possible to establish associations on the actual impact of a given response after 6 or 12 months treatment on the evolution, therapy and prognosis of patients.

We consider that our study shows the need to further investigate clinical and prognosis implications of HAART in children because, up to now, many recommendations on pediatric HIV management are extrapolated from adult-oriented studies.

In conclusion, discordant response in the pediatric population in our clinic is >50% 12 months after beginning HAART, showing a higher frequency than reported for adults. These discordant responses were not correlated

| Table 2. Virologic and immunologic responses follow-up in pediatric HIV patients after 6 and 12 months of beginning HAART at Hospital Infantil de Mexico Federico Gomez |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Response type at 12 months HAART | 1 VS/IS n =15 (%) | 2 VF/IF n = 16 (%) | 3 VS/IF n = 6 (%) | 4 VF/IS n = 19 (%) |
| 1 VS/IS | 6 (40) | 5 (31.25) | 2 (33.3) | 4 (21) |
| 2 VF/IF | 1 (6.67) | 2 (12.5) | 2 (33.3) | 4 (21) |
| 3 VS/IF | 5 (33.33) | 1 (6.25) | 2 (33.3) | 5 (26.32) |
| 4 VF/IS | 3 (20) | 8 (50) | 0 (0) | 6 (31.58) |

IS, immunologic success; VS, virologic success; IF, immunologic failure; VF, viral failure; HAART, highly active antiretroviral therapy (FIGURE 1)
with higher morbidity during the follow-up period. In spite of being common, clinical repercussion of HAART discordant response is still uncertain. More studies are required in order to obtain a consensus about discordant response association with therapeutic failure. We advise the cautious interpretation of discordant responses.

References


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