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Structured Intermittent Therapy with Seven-day Cycles of HAART for Chronic HIV Infection: A Pilot Study in São Paulo, Brazil

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ABSTRACT

In the last 6 years, an impressive impact of the highly active antiretroviral therapy (HAART) on survival and morbidity in HIV-1–infected individuals has been attained. However, their prolonged use may induce metabolic adverse effects such as lipodistrophy, hypertension, diabetes mellitus, osteopenia and hyperlipidemia. Recently, new strategies such as short-cycle structured intermittent therapy (SIT; 7 days without therapy followed by 7 days with HAART) have been suggested. We tested this strategy in seven (four women and three men; mean of age 39 of years) HIV-positive individuals, all of whom had $CD4^+$ T cell counts greater than 500 cells/mm^3 and undetectable plasma viral load for at least 2 years. Our results indicated no opportunistic diseases or CD4 cell count decrease over a mean follow-up of 26 months. No plasma viral replication was detected in five of seven cases. There was a decrease in triglyceride levels to normal range (not statistically significant), but no modification of cholesterol levels. Thus, we recommend a larger clinical trial to determine if SIT is cost effective in developing countries.

INTRODUCTION

In the last 6 years, with highly active antiretroviral therapy (HAART), Brazil has experienced a prolongation of survival, a decrease in the number of opportunistic infections, and an improvement in the quality of life of HIV-infected individuals.[1,2] In 1993, a federal law determined that the antiretroviral medications should be released free of cost by public health providers for all Brazilians with HIV/AIDS based on local guidelines. The Ministry of Health, through the National Coordination of DST/Aids,[3] developed programs for monitoring laboratory tests ($CD4^+$ cell counts and viral load quantification) and distribution of the medications at the national level.

Mathematical models demonstrated that if the viral replication was totally suppressed, 72 years of treatment would be necessary for complete HIV eradication in the reservoirs.[4] In fact, despite HAART efficacy, with undetectable viral loads for many years, some viral replication persists, and the therapy should continue lifelong.[5] Thus, HIV/Aids is now characterized as a chronic disease that can be controlled in many, but prolonged HAART exposure may drive the appearance of collateral effects, such as lipid and bony alterations, anomalous corporal fat redistribution, as well as cardiac toxicity.[6]

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Because of this, treatment strategies that avoid constant use of these drugs are desirable.[7,8] It has been demonstrated that short-cycle structured intermittent therapy (SIT; 7 days without therapy followed by 7 days with HAART) with a zidovudine, lamivudine, or stavudine plus efavirenz regimen maintained suppression of plasma HIV viremia.[9,10] In this study, we determined the safety and effectiveness of the SIT regime in HIV-infected carriers in São Paulo.

MATERIALS AND METHODS

Patient

Seven patients were selected from 223 HIV-infected individuals who have been followed at the Secondary Immunodeficiencies, Dermatology Department at the HC-FMUSP. These patients on regular treatment with HAART for least 2 years, had undetectable plasma viral load (< 80 copies per milliliter) for at least 2 years, had T $CD4^+$ cell counts above 500 cells/mm^3 for at least 12 months, and had never developed opportunistic infections or neoplasia. The participants had support from nurses, nutritionists, and psychologists, as do all patients in follow-up, and the HC-FMUSP ethical board approved the protocol and written informed consent was obtained in all participants. The seven patients, four women and three men, with a mean of age of 39 years, were followed for 12–42 months, mean 26 months (Table 1), and self-reported HIV infection by sexual transmission route. All antiretroviral drugs were suspended at the same time during the time off therapy. The adherence was evaluated by a simple questionnaire, as described elsewhere.[11] Analysis of variance for either for interpatient or intrapatient, variation involved nonparametric Mann-Whitney's test.

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Methods

Blood was collected on the fifth day without therapy every 4 months for all evaluations.

Table 1. Laboratory Parameters for Patients Participating in a Clinical Trial of SIT at Seven Days Without Followed by Seven Days with Antiretroviral Therapy

Case	*Gender/ age*	*HAART Pre-SIT*	*Nadir $CD4^+$ T cells pre-HAART*	*$CD4^+$ T cells pre-SIT*	*VL HIV Pre-HAART*	*Months of HAART prestudy*
01	M/44	AZT, 3TC, EFZ	628	731	120000	48
02	M/47	D4T, 3TC, EFZ	336	840	190	60
03	F/32	AZT, 3TC, EFZ	336	900	NA	62
04	F/36	AZT, 3TC, EFZ	379	879	37000	60
05	F/46	AZT, 3TC, NVP	389	618	NA	96
06	F/46	AZT, 3TC, EFZ	409	1216	1216	48
07	M/32	AZT, 3TC, EFZ	319	639	270000	48

M, male; F, female; Age, years; SIT, Short-cycle structured intermittent therapy; HAART, highly active anti-retroviral therapy; VL, viral load expressed in copies per milliliter; NA, not available.

TABLE 2. LABORATORY DATA AFTER SIT AT SEVEN DAYS WITHOUT FOLLOWED BY SEVEN DAYS WITH HAART

Case	*HAART during SIT*	*Nadir CD4$^+$ T cells post-SIT*	*Last CD4$^+$ T cells post-SIT*	*Last VL HIV post-SIT*	*Months of SIT*
01	AZT, 3TC, EFZ	998	1221	< 80	28
02	D4T, 3TC, EFZ	457	492	3120	27
03	AZT, 3TC, EFZ	681	981	< 80	24
04	AZT, 3TC, EFZ	614	790	< 80	22
05	AZT, 3TC, NVP	484	484	< 80	12
06	AZT, 3TC, EFZ	901	1277	928	42
07	AZT, 3TC, EFZ	685	685	< 80	25

SIT, Short-cycle structured intermittent therapy; HAART, highly active anti-retroviral therapy; T CD4 cells counts expressed cells/mm^3; VL, viral load expressed in copies per milliliter.

CD4$^+$ T-cell counts were done with commercial kits, and counted by FACS equipment (XL model, Coulter, USA). RNA viral load was determined using polymerase chain reaction (PCR) commercial kits (HIV monitor Roche Diagnostic, Hercules, CA), with a detection limit of 400 copies per milliliter. Visual reading was also performed, which may be able to detect a single viral copy in the computer software. Over 5000 copies per milliliter was considered to be viral rebound.

RESULTS

The SIT group maintained viremia suppression and CD4$^+$ T-cell counts did not decrease. Only case 3 showed side effects in the final months of the trial because of efavirenz, and was switched to another regimen. Two cases, 2 and 6, had blips in their plasma viral load during the follow-up, but these were below 5000 copies per milliliter (Table 2). Visual observation in computer software showed no copies in the 5 cases with full suppression of plasma viral load, indicating probably less than 1 copy per milliliter. The triglycerides and cholesterol levels were not statistically different after SIT (ranging from 180 to 245 before SIT, mean 201 mg/dL; and ranging from 186 to 228, mean 206 mg/dL after SIT), but a clear decrease in the former (from 170 to 134 mg/dL) was noted (Table 3).

DISCUSSION

After a mean of almost 2 years of follow-up, none of seven patients showed any progression of HIV disease on a 7-day SIT regimen. Although two patients showed blips in their plasma viral load, the CD4$^+$ T-cell counts were maintained during this time. In addition, there were no significant alterations in triglycerides or cholesterol levels. However, a decrease in the first was noted.

TABLE 3. TRIGLYCERIDES LEVELS AMONG PATIENTS USING SEVEN DAYS ON FOLLOWED BY SEVEN DAYS OFF STRATEGY

Case	*Triglycerides pre-HAART*	*Triglycerides pre-SIT*	*Triglycerides post-SIT*
01	184	65	70
02	169	336	173
03	208	85	97
04	229	155	140
05	67	239	166
06	99	187	113
07	99	127	278
Mean	150	170	134

HAART, highly active antiretroviral therapy; SIT, structured intermittent therapy.

The chronic and continuous use of antiretroviral (ART) drugs constitutes a considerable economic problem for the country. In 2003, approximately 150,000 people used ART daily in Brazil. The cost of this treatment is approximately 232 million American dollars, and it would be even more expensive if the country did not possess the control and domestic production of several anti-HIV drugs.[12]

The SIT patients used half of the prescribed medication. In one study of patients in our clinic,[11] approximately 40%–50% of HIV-infected patients presented with viral loads below the detection limit and $CD4^+$ T-cell counts above 500 cells/mm^3. HAART was recommended for these patients based upon national guidelines current at the time. New modifications have been made to the guidelines, and currently they probably would not be considered for initiation of therapy.[13] However, once begun, suspension of HAART is not usually recommended. Thus, a considerable number of patients still on therapy despite high CD4 counts and low viral load would be potential subjects for SIT, with a large savings on medication costs for the country.

Our data agree with other pilot studies of 7-day SIT cycles in highly selected subjects,[9,10] since no decrease in $CD4^+$ T-cell count, rebound in the viral load, nor HIV disease progression were seen among our patients. However, a clear possibility of blips in the viral load may happen during the follow-up in some patients.[10] Finally, our data with longer follow-up and using local resources in a developing country adds support for larger clinical trails to access the feasibility of SIT strategy.

REFERENCES

1. Casseb J, Pereira Junior LC, Silva GL, Medeiros LA. Decreasing mortality and morbidity in adult AIDS patients from 1995 to 1997 at the Institute of Infectious Diseases "Emílio Ribas" (IIER), São Paulo, Brazil. AIDS Patient Care STDs 1999;13:213–214.
2. Casseb J, Orrico GS, Feijo RDP, Guaracy L, Medeiros LA. Lack of prior antiretroviral therapy is strongly associated with death among hospitalized adults with AIDS at the Institute of Infectious Diseases "Emílio Ribas," São Paulo, Brazil. AIDS Patient Care STDs 2001;15:271–275.
3. AIDS: Boletim epidemiológico. Ministério da Saúde/Programa Nacional de DST/AIDS Brasília, Brasil, Ano XVII, 2004, Número 01.
4. Hamer DH. Can HIV be Cured? Mechanisms of HIV persistence and strategies to combat it. Curr HIV Res 2004;2:99–111.
5. Pierson T, McArthur J, Siliciano RF. Reservoirs for HIV-1: Mechanisms for viral persistence in the presence of antiviral immune responses and antiretroviral therapy. Annul Rev Immunol 2000;18:665–708.
6. Gulick RM. Structured treatment interruption in patients infected with HIV: New approach to therapy. Drugs 2002;62:245–253.
7. Can A, Samaras K, Burton S, et al. A syndrome of peripheral lpodystrophy, hyperlipidemia and insulin resistance due to HIV protease inhibitors. AIDS 1998;12:F51–F58.
8. Hogg RS, Havlir D, Miller V, Montaner JSG. To stop or not to stop: That is the question, but what is the answer? AIDS 2002;16:787–789.
9. Dybul M, Chun TW, Yoder C, et al. Short-cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: Effects on virologic, immunologic, and toxicity parameters. Proc Natl Acad Sci USA 2001;98:15161–15166.
10. Dybul M, Nies-Kraske E, Dewar R, et al. A proof-of-concept study of short-cycle intermittent antiretroviral therapy with a once-daily regimen of didanosine, lamivudine, and efavirenz for the treatment of chronic HIV infection. J Infect Dis 2004;189:1974–1982.
11. Brigido L, Rodrigues R, Casseb J, Custodio RM, Fonseca LA, Sanchez M, Duarte AJ. $CD4^+$ T-cell recovery and clinical outcome in HIV-1-infected patients exposed to multiple antiretroviral regimens: Partial control of viremia is associated with favorable outcome. AIDS Patient Care STDs 2004;18:189–198.
12. Galvão G. Access to antiretroviral drugs in Brazil. Lancet 2002;360:1862–1865.
13. MINISTÉRIO DA SAÚDE. Secretaria de Vigilância em Saúde Programa Nacional de DST e Aids. Recomendações para Terapia Anti-Retroviral em Adultos e Adolescentes Infectados pelo HIV, 2004. www.aids.gov.br (Last accessed April 10, 2005).

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