Gastrostomy Tube Insertion for Improvement of Adherence to Highly Active Antiretroviral Therapy in Pediatric Patients With Human Immunodeficiency Virus

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ABSTRACT. *Objectives.* **Newer combination antiretroviral therapies used to treat human immunodeficiency virus (HIV)-infected individuals have resulted in dramatic delays in HIV progression, with reduction in mortality and morbidity. However, adherence to highly active antiretroviral therapy (HAART) may be problematic, particularly in HIV-infected children. Reasons for nonadherence include refusal, drug tolerability, and adverse reactions. We assess: 1) the potential benefits of gastrostomy tube (GT) for the improvement of adherence to HAART in HIV-infected children, and 2) the factors that may result in improved viral suppression after GT placement.**

Methods. **The medical records of 17 pediatric HIV-infected patients, in whom GT was used to improve HAART adherence, were retrospectively reviewed for clinical and laboratory parameters. Each record was reviewed for the period of 1 year before and after GT insertion. The main outcome parameters were virologic (plasma HIV RNA polymerase chain reaction quantification) and immunologic (CD4 cell counts). Documentation of adherence to medications in medical records was also assessed during the study. Parental questionnaires were used to determine GT satisfaction and medication administration times. The Wilcoxon rank sum test was used to assess change in viral load (VL) and CD4 cell percentages.**

Results. **GT was well-tolerated with minor complications, such as local site tenderness, reported by 4 patients (23%). Before GT insertion, only 6 patients (35%) were documented as being adherent, compared with all patients after GT insertion. Ten patients (58%) had ≥2 $\log_{10}$ VL decline after GT insertion (median: 3.2 $\log_{10}$), compared with 7 patients (42%) who had ≤2 $\log_{10}$ VL decline (median: 1.27 $\log_{10}$). Both groups of patients (responders and nonresponders) did not differ significantly in baseline parameters, such as VL, CD4 cell percentages, or previous drug therapy. However, in all 10 patients with ≥2 $\log_{10}$ VL decline, therapy was changed at the time of or soon after GT insertion (median: .8 months; range: 0–6 months), compared with 7 patients with <2 $\log_{10}$ VL decline who had therapy changed before GT insertion (median: 3.2 months; range: 1–8 months). Parental questionnaires reported significantly shorter medication administration times after GT insertion, with 70% of patients taking >5 minutes before GT, compared with 0% after GT. Questionnaires indicated satisfaction with GT, with perceived benefits being reduced medication administration time and improved behavior surrounding taking medications.**

Conclusions. **GT is well-tolerated in pediatric HIV-infected patients and should be considered for selected patients to overcome difficulties with medication administration and to improve adherence. For maximal virologic response, combination therapy should be changed at the time of GT insertion.** *Pediatrics* **2000;105(6). URL: http://www.pediatrics.org/cgi/content/full/105/6/e80;** ***gastrostomy tube, pediatric human immunodeficiency virus infection, highly active antiretroviral therapy.***

ABBREVIATIONS. HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; GT, gastrostomy tube; CMH, Children's Memorial Hospital; UCSD, University of California, San Diego Medical Center; VL, viral load.

The efficiency of the newer combination antiretroviral therapies in treating human immunodeficiency virus (HIV)-infected individuals is unprecedented. Dramatic delays in HIV progression, improved survival, and decreased morbidity have occurred in patients taking highly active antiretroviral therapy (HAART).[1] A stepwise reduction in morbidity and mortality occurs with increased intensity of antiretroviral therapy, particularly protease inhibitors.[1] However, adherence has been essential in achieving maximal viral suppression and preventing the emergence of drug-resistant mutants. Adherence levels of over 95% have been associated with virologic suppression; success rates fall sharply with decreasing levels of adherence.[2] Adherence ranges from 46% to 88% by self-report[3,4] or plasma drug analysis,[5] suggesting that the magnitude and durability of HAART will be compromised. Furthermore, adherence was a good predictor of effective viral suppression.[6–8] Adherence to HAART is determined by multiple factors including the patient's neurological and mental attitude, drug palatability, dosing frequency, amount of drug, relation of dosage to meals, toxicity, and adverse effects. These factors are often more pronounced and problematic in children.[9] For example, protease inhibitor use in children is associated with adverse events, particularly gastrointestinal, and resulted in discontinuation of therapy in 10% to 14% of patients.[10,11] It has been suggested

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that great efforts will be needed to overcome the barriers contributing to poor adherence in children.[12]

Gastrostomy tubes (GTs) have been relatively well-tolerated and used successfully in both HIV-infected adults and children for long-term nutritional supplementation.[13–15] An increase in complications, mostly wound infection, was reported in HIV-infected children, compared with non-HIV-infected control patients with GT.[16] With the advent of HAART and the need to optimize adherence, we introduced GT in certain patients in whom adherence was a problem, hoping to achieve more effective and durable viral suppression. We report our retrospective evaluation of this approach and analysis of the factors that may influence effective viral suppression with GT.

METHODS

Subjects

A retrospective medical record review of all HIV-infected children who had GT insertion for improvement of medication adherence between January 1995 and December 1998 was performed in 2 centers: Children's Memorial Hospital (CMH), Chicago, Illinois and the University of California, San Diego Medical Center (UCSD), San Diego, California. Each record was reviewed for the period of 1 year before and 1 year after GT insertion. Data collected included demographic information, GT insertion method and complications, antiretroviral therapy and adherence, and reasons for stopping antiretroviral therapy.

Virologic and Immunologic Data

Viral load (VL) measurements and CD4 cell counts at each site were generally performed every 3 months. VL was measured by plasma HIV RNA quantification using the polymerase chain reaction assay (Roche Amplicor; lower limit of detection 400 copies/mL). CD4 cell counts were measured by T-lymphocyte subset analysis using dual-color flow cytometry (Cytoron, Ortho Diagnostics, Raritan, NJ [CMH]; Facscan, Becton Dickinson, Mountain View, CA [UCSD]).

Adherence Data

Physician or nurse documentation at each visit was reviewed for adherence to HAART. Patients were regarded as nonadherent in a 1-year period before GT if they had at least 2 visits where nonadherence was documented. In a similar fashion, adherence was classified in the year after GT insertion.

Parental Questionnaire

At a post-GT insertion visit, parents at both sites were asked to complete a questionnaire aimed at determining satisfaction with GT placement in addition to perceived potential advantages and disadvantages of the procedure. Responses to the question regarding time taken to administer individual medications before and after GT placement were grouped into 3 categories: <2 minutes, 2–5 minutes, and >5 minutes. In 1 center (CMH), a control group without GT was also surveyed for time taken to give medications. Control patients were identified as those in whom adherence was not a problem and were matched for age (1–4 years $\pm$ 6 months and >4 years $\pm$ 1 year) and therapy (similar classes and number of medications).

Statistical Analysis

Patients were subdivided into 2 groups for purposes of analysis: responders were classified as having a log decline ≥ 2 in viral copy number after GT placement, and nonresponders were classified as having log decline <2 in VL. VL change was defined as the difference between VL closest to 1-year post-GT minus VL closest to or before GT placement. For purposes of calculation, an undetectable VL was defined as <400 copies/mL or $\log_{10}$ 2.6. Data were maintained and analyzed in SPSS version 6.14 (SPSS, Inc, Chicago, IL). Because of the small sample size, nonparametric analysis using the Wilcoxon rank sum test was used to assess the changes in VL and CD4 cell counts. Quantitative variables were reported by their median values.

RESULTS

Subjects

Records of 17 HIV-infected children (6 boys and 11 girls) who had GT inserted primarily for medication administration are included in this report (11 from CMH and 6 from UCSD). All children were perinatally infected. The median age at time of GT placement was 2.9 years (range: 1.25–11.8 years). Nine patients were black (53%), 5 were Hispanic (30%), and 3 were white (17%).

Eleven patients were severely symptomatic (Centers for Disease Control and Prevention clinical category C), 1 patient was moderately symptomatic (clinical category B), and 5 patients were mildly symptomatic (clinical category A).[17] In addition, 10 patients had severely suppressed CD4 counts (immune category 3), 1 patient had moderate suppression (immune category 2), and 6 patients had mild suppression (immune category 1).

GT Placement and Follow-up

Ten children had GT placed for medication delivery alone, and 7 had GT placed for medication treatment and nutrition. In 9 patients, GT placement (53%) was performed by an interventional radiologist using a percutaneous fluoroscopic technique with sedation and local anesthesia (site specific to CMH). Eight GT placements were performed using general anesthesia, 7 by a gastroenterologist (35%) using a percutaneous endoscopic technique and 1 by a pediatric surgeon. Long external tubes were initially placed to allow for adequate healing and tract formation. These were converted to the button GT after 2 to 3 weeks (Fig 1). Buttons were changed as necessary (if accidentally dislodged or for replacement with larger sized tubes) and remained in place for the duration of GT use. None of the patients received either prophylactic antibiotics or acid-blocking agents. Four patients (23%) reported local site tenderness in the 2 months after GT insertion. One patient developed stomal cellulitis within 2 months of GT insertion and was treated with intravenous

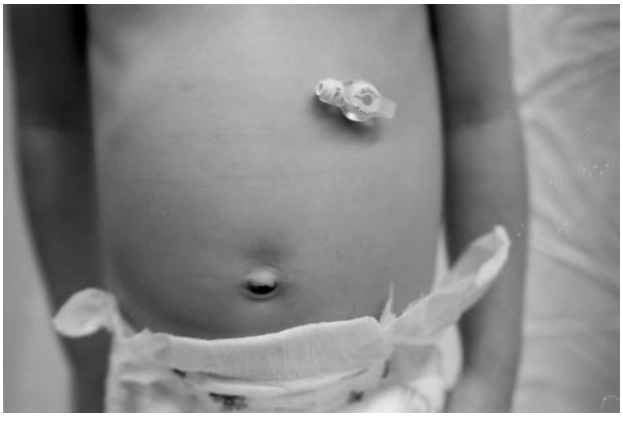

Fig 1. GT button on a child's abdomen.

antibiotic therapy. None of the patients who had a complication required GT removal.

Parental questionnaires suggested general satisfaction with GT. One family believed that the appearance of the GT was a potential disadvantage because it was a "visual representation of disease." Only 1 family reported lifestyle changes in an older child who was unable to participate in gymnastics because of the GT. No families reported problems with other activities, such as swimming.

Adherence to HAART

In the year before GT insertion, good adherence to HAART was recorded in 6 patients (35%), 7 were nonadherent (41%), and in 4 patients (23%) adherence data were not documented in the patient's chart. All 17 patients were noted to be adherent to therapy after GT placement.

Virologic and Immunologic Response

Seventeen patients had complete viral and immunologic data pre- and post-GT insertion. Table 1 summarizes and compares responders (≥2 logs reduction in VL) and nonresponders (<2 logs reduction in VL). Ten patients (59%) had ≥2 log change in VL and 7 patients (41%) had <2 log change in VL. Responder and nonresponder groups did not differ significantly in baseline VL (median: 5.5 and 5.24 logs, respectively; Wilcoxon rank sum, $P = 1$) and CD4 percentage (7% and 10%, respectively; Wilcoxon rank sum, $P = .6$). Protease inhibitor naivete and use of double protease inhibitors with therapy change were also similar in both groups. Median VL decrease in the responders group was 3.2 logs (range: 2.1–3.5 logs) compared with 1.27 logs (.63–1.6 logs) in the nonresponders group ($P = .0008$).

Eight of 10 patients (80%) in the responder group had undetectable VLs (<400 copies/mL) compared with none in the nonresponders group ($P = .02$). Median CD4% changes were not statistically different between responders and nonresponders (median of +7% [range: 2%–28.5%) and +10% [range: 3%–23%], respectively). Timing of medication change in relation to GT placement showed a statistically significant difference between the groups.

Change to new antiretroviral drugs occurred at a median of .8 months (range: 0–6 months) after GT placement in the responders group compared with a median of 3.2 months (range: 1–8 months) before GT placement in the nonresponder group ($P < .05$).

Time Taken to Give Medications

Parents of patients with GT reported significantly shorter medication administration time after GT insertion (Fig 2). Before GT placement, 70% reported taking >5 minutes to administer medications, compared with 0% after GT placement (paired t test, $P = .001$). Post-GT times to administer medications did not significantly differ from the control group of patients who were age- and therapy-matched (Fig 2). Parental questionnaires indicated that all were satisfied with the GT. The perceived benefits of GT were reduction in time for drug administration with only minor complications and marked improvement of behavior surrounding taking the medications.

DISCUSSION

This study suggests that GT placement in HIV-infected children with medication adherence problems results in improved adherence and ease of administration of medications, which facilitates effective viral suppression with HAART; this is particularly evident if therapy is changed during or shortly after GT placement. In addition, GT placement was generally well-tolerated. We were especially impressed by the low rate of complications in the 9 patients in whom the GT was placed by an interventional radiologist. This procedure did not involve general anesthesia, and in most cases, the patient was able to go home in <24 hours after the procedure.[18]

Adherence with medication in children is a complex issue. Reasons for nonadherence are multifactorial and related to the large number (or amount) of medications, palatability, frequent dosing, need to match dosing time with meals, and frequent side effects. In addition, administering medication to a child often presents special challenges because the child may be unaware of the purpose of the medication and may be reluctant to take unpleasant-tasting tablets or syrups.[6] Parental health (eg, depression, altered mental status, and substance abuse), guilt, and ability to give medications to their child (and to themselves) are other unique factors affecting adherence for HIV-infected children.

In our small cohort, adherence to therapy was noted to be 100% after GT placement. GT placement

TABLE 1. Viral and Immunologic Response in Responders and Nonresponders

	Responders (≥2 Log Change in VL)	Nonresponders (<2 Log Change in VL)	*P* Value
Number	10	7	
Median baseline log VL before GT (range)	5.5 (4.75–5.87)	5.24 (4.80–6.67)	1
Median log VL change after GT (range)	−3.2 (2.1–3.5)	−1.27 (.63–1.6)	.0008
Undetectable VL* (%)	8 (80%)	0 (0%)	.02
Median baseline CD4% before GT (range)	16% (1–46)	23% (1–50)	.6
Median CD4% change after GT (range)	+7% (2%–28.5%)	+10% (3%–23%)	.2
PI naive at time of GT (%)	5 (50%)	4 (57%)	.9
Therapy change to double PI regimen (%)	4 (40%)	3 (42%)	.4
Median time of medication change in relation to GT in mo (range)	.8 mo after insertion (0–6 mo after insertion)	3.2 mo before insertion (1–8 mo before insertion)	.005

PI indicates protease inhibitor.
* <400 copies/mL.

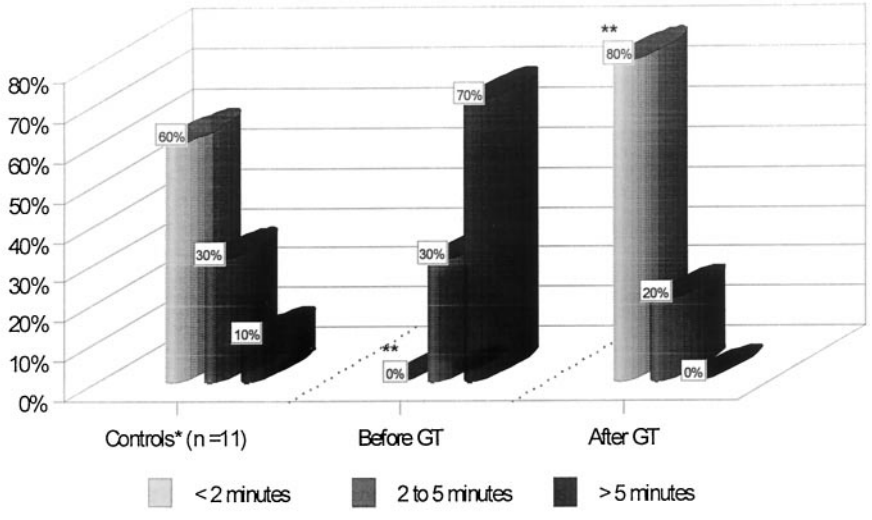

Fig 2. Comparison of time to administer medications before GT placement, after placement, and in the control group.

also allowed a reduction in the time taken to give the medications to levels comparable to age- and therapy-matched controls in whom adherence was not a problem.

Furthermore, GT placement allowed for the use of more potent antiretroviral drugs, eg, Ritonavir, which are often unpalatable and difficult to administer to younger children. Complications from the procedure were transient and minor (with only 1 patient developing stomal cellulitis that required intravenous antibiotics for resolution) and comparable to those reported for GT placement for nutritional supplementation in HIV-infected patients.[13–15] It is possible that our observed improvement in time to administer medications is biased in favor of GT because of the retrospective parental survey regarding pre-GT experiences. However, the pre-GT and post-GT differences are impressive and suggest that an increase in time taken to give medication may be an important warning signal of potential adherence problems. Parents' reduction in difficulties surrounding medication administration after GT placement resulted in perceived advantages (eg, better behavior and fewer fights) and improved the parent–child relationships while reducing family stress.

At 1-year post-GT insertion nearly 59% of patients had ≥2 log VL decrease (responder group). Both responders and nonresponders were similar in baseline VL, protease inhibitor exposure, and use of double protease inhibitor therapy. Yet responders were more likely to have changed therapy at or soon after GT placement, whereas nonresponders had no therapy changes after GT placement. These data suggest that to minimize the impact of viral resistance secondary to nonadherence, HAART should be changed immediately after GT placement. Thereafter, the improved adherence will minimize development of resistance to the new combination. We found that the CD4 lymphocyte percentage changes in responders and nonresponders were not different (7% and 10% increase, respectively). One possible explanation for this may be related to the relatively short period of follow-up post-GT insertion, which may have been insufficient to observe an immunologic response. Alternatively, a disconnect between viral response and CD4 cell response has been previously reported.[19–21] Several mechanisms for this phenomenon have been suggested including the possibility that protease-resistant mutants may have an altered pathogenicity related to lack of viral fitness.[22–24]

CONCLUSION

In summary, GT placement was safe and well-tolerated in HIV-infected children and resulted in improved HAART adherence. In addition, when combination therapy was changed at or soon after GT insertion, the virologic response was further improved. GT insertion significantly reduced parent-reported times for medication administration and, therefore, may have the potential to improve the quality of life of HIV-infected children and their families.

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