JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eHIV Review

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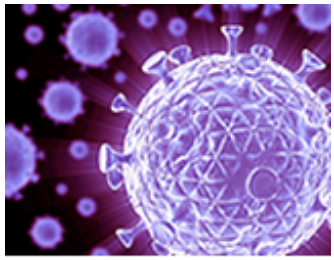

VOLUME 1, NUMBER 11

Editor's Note: *Please visit our new webcast & podcast, titled "Samantha, A Life with HIV: Optimizing Therapy in HIV Subpopulations". Originally presented at the 2012 International AIDS Conference, we share a brief view into the many challenges facing patients with HIV. During the course of this program, you will follow Samantha, from diagnosis at a young, troubled age, through maturity and into adulthood, narrated by filmmaker John Waters.*

Emerging Promises and Challenges with the Use of Antiretroviral Therapy for Prevention of HIV Transmission

In this Issue...

In this issue, we review the results of several key studies that have evaluated the use of antiretroviral agents for HIV prevention. The HPTN 052 study demonstrated that early initiation of highly active antiretroviral therapy (HAART) could decrease HIV transmission in serodiscordant couples. Several studies of pre-exposure prophylaxis (PrEP) showed that the anticipatory use of antiretroviral therapy by high-risk people without HIV infections could decrease HIV incidence. Unfortunately, other studies did not demonstrate efficacy. The major reason for the variation in results appears to be associated with medication adherence, but other factors, such as mucosal biology, are also under investigation.

Although these first-generation studies of antiretroviral agents for preventing HIV have proved that the concept can work, additional research is under way to determine optimal dosing strategies and the most appropriate medications for specific populations. The initial results led the US Food and Drug Administration to approve the use of daily coformulated tenofovir plus emtricitabine for PrEP in high-risk populations. More guidance is available at the Centers for Disease Control and Prevention (CDC) Web site.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Discuss new findings on the use of antiretroviral agents for primary HIV prevention
- Describe the impact of early initiation of treatment on HIV transmission
- Identify appropriate candidates for pre-exposure prophylaxis for HIV prevention

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Three central ideas emerged from our needs assessment. In order to provide optimal treatment to patients with HIV:

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- Clinicians caring for patients with HIV need current information about: appropriate treatment and maintenance of care…guidance for treating comorbidities…and information about emerging findings for treating HIV-associated neurocognitive disorders (HAND)
- The need for more information on HIV topics including updated guidelines for HIV, treating older patients with HIV, managing patients with comorbidities and coinfections, treatment and sequencing strategies for maximizing future therapeutic options, and new and emerging agents for HIV
- Treating comorbidities in patients with HIV, especially among people older than age 50

INTENDED AUDIENCE
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THIS ISSUE

Program Directors

Richard Moore, MD, MHS
Professor of Medicine
Director, Moore Clinic for HIV Care
Divisions of Infectious Diseases and Clinical Pharmacology
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Michael Melia, MD
Assistant Professor of Medicine
Associate fellowship Program Director
Division of Infectious Diseases
The Johns Hopkins University School of Medicine
Baltimore, Maryland

GUEST AUTHOR OF THE MONTH

Commentary & Reviews:
Kenneth H. Mayer, MD
Director of HIV Prevention Research and Infectious Disease Attending Physician
Beth Israel Deaconess Medical Center
Professor of Medicine
Harvard Medical School
Medical Research Director
The Fenway Institute
Fenway Health
Boston, Massachusetts

Guest Faculty Disclosure

Kenneth H. Mayer, MD, has disclosed that he has received grants/research support from Bristol-Myers Squibb, Gilead and Merck.

Unlabeled/Unapproved Uses

The author has indicated that he will reference the unlabeled/unapproved uses of tenofovir gel for HIV prevention.

Program Directors' Disclosures

COMMENTARY

Despite improvements in treatment, and primarily because of ongoing unprotected sex, worldwide, more than two million people annually have become infected with HIV over the past few years, with more than 50,000 new infections each year in the United States alone.[1,2] Yet within the past three years, an evidence base has been developed suggesting that antiretroviral agents can play a significant role in curbing the spread of HIV. The first proof of concept was the Centre for the AIDS Program of Research in South Africa (CAPRISA) 004 study, which demonstrated that pericoitally administered 1% tenofovir gel decreased HIV by 39% in at-risk South African women.[3] This was followed shortly thereafter by the Pre-exposure Prophylaxis Initiative (iPrEx) study (discussed by

Grant and colleagues in this issue), which found that the daily use of oral coformulated tenofovir plus emtricitabine was associated with a 44% reduction in HIV incidence in an international cohort of men who have sex with men (MSM). Within the next year, additional studies demonstrated the efficacy of oral pre-exposure prophylaxis (PrEP) in several at-risk male and female African heterosexual populations (Baeten and coworkers, Thigpen and collaborators; both reviewed in this issue). Complementing these studies of topical and oral chemoprophylaxis were the findings of the HIV Prevention Trials Network (HPTN) 052 (described by Cohen and colleagues in this issue), which demonstrated that earlier initiation of highly active antiretroviral therapy (HAART), at CD4 cell counts between 350 and 550 cells/mm^3, decreased HIV transmission in serodiscordant couples. During the same period of time, however, several chemoprophylaxis studies were not successful in demonstrating efficacy: the FEM-PrEP trial of young African women (reviewed by Van Damme and associates in this issue), which evaluated the combination of oral daily tenofovir plus emtricitabine, and the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study[4] of a similar population, which evaluated daily oral tenofovir alone and daily topical tenofovir gel. As of the end of January 2013, a comparison of oral daily tenofovir plus emtricitabine in the VOICE trial was still ongoing.

So, how do we deal with these diverse, sometimes discrepant findings in the PrEP studies? It is clear that in the trials for which adherence data are available, differential patterns of use in varying populations were a major part of the divergent results across the studies. Of participants assigned to active medication, when drug levels were evaluated in the study with the greatest efficacy—that is, Partners PrEP—tenofovir was detected in 80% of the samples, compared with the results of FEM-PrEP, in which the drug was detected in about 25% of the women.[5] It is possible that cultural norms regarding pill taking and perceived side effects may explain some of the differences in adherence between the populations.[5] Other factors may be relevant as well, such as the presence of intercurrent genital inflammation caused by other sexually transmitted infections (STIs) or sexual trauma.[6] Differences in mucosal pharmacology might also play a role, because after oral dosing, tenofovir concentrations are at least 1 log lower in vaginal than in rectal secretions,[7] suggesting that women may have to be more adherent to achieve a protective benefit comparable to that in MSM.

The PrEP studies that have been completed suggest that oral tenofovir plus emtricitabine is generally safe and well tolerated. As discussed in the 2010 study by Grant and associates, a small number of trial participants experienced nausea or diarrhea that tended to be mild and self-limited. Participants rarely experienced low rates of nephrotoxicity, but a statistically significant, although not clinically meaningful, change in bone mineral density (BMD) was reported in a minority of participants randomized to tenofovir-based PrEP compared with placebo.[8] Longer-term studies are warranted to determine whether any of these safety signals become clinically meaningful. According to the reviews by Grant and coworkers, and Baeten and associates, other potential concerns, such as significant behavioral disinhibition or the selection for tenofovir- or emtricitabine-resistant viruses in seroconverters, were not observed in the context of the carefully monitored clinical trials.[9] Although adherence was suboptimal in some of the studies, it was sufficient to demonstrate efficacy in several key populations.[10] The short-term safety data, coupled with efficacy data, were sufficient for the US Food and Drug Administration to approve tenofovir plus emtricitabine for chemoprophylaxis in July 2012.[11]

Other studies currently under way may help address some of the outstanding questions. The remaining comparison in the VOICE trial will help to address the relative efficacy of tenofovir plus emtricitabine for prophylaxis in women, and the measurement of drug levels in participants randomized to all three active treatment arms will help to inform the role of nonadherence in decreased efficacy. The Follow-on African Consortium for Tenofovir Studies (FACTS) 001 trial is under way in South Africa to evaluate whether the CAPRISA 004 results can be replicated, given the lack of efficacy reported in the VOICE trial.[3] A study will soon be completed in Thailand[14] that will evaluate whether injecting drug users might benefit from oral PrEP. The optimal frequency of PrEP dosing is not yet known, since animal data suggest that intermittent PrEP may be almost as effective.[12]

One preliminary study of MSM and female sex workers in Kenya and Uganda suggested that some high-risk individuals often missed a postcoital dose when event-driven PrEP was evaluated.[13] Other studies are under way in the United States, South Africa, Thailand,

and France to assess different dosing schedules for intermittent PrEP in diverse populations (www.avac.org).[14] Although the VOICE trial did demonstrate the efficacy of daily vaginal tenofovir gel use for women, it is conceivable that rectal microbicides might prove to be efficacious for MSM and women who engage in anal sex, given the potential for increased penetration of rectally applied gels (because of the single layer of protective columnar epithelium and larger virtual space compared with the cervicovaginal compartment) and the increased likelihood that lubricants might be routinely used for anal intercourse compared with vaginal intercourse.[15,16] Lastly, although the initial oral and topical PrEP studies focused on tenofovir plus or minus emtricitabine, studies of other agents, including nonnucleoside reverse transcriptase inhibitors such as dapivirine, entry inhibitors such as maraviroc, and newer integrase inhibitors, are now under way to evaluate whether longer-acting formulations, delivered as intravaginal rings or injectable agents, may obviate some of the challenges of maintaining high levels of product adherence.[17]

Despite the promising findings of recent PrEP studies, it is unclear whether chemoprophylaxis alone will be sufficient to quickly arrest the spread of HIV, given the relatively slow uptake of the intervention among the highest-risk populations.[18] Moreover, according to the review herein by Cohen and collaborators, the findings of HPTN 052 suggest that earlier diagnosis of HIV and initiation of treatment may be particularly promising factors in decreasing the incidence of disease. Several ecological studies in different populations have correlated wider access to HAART with decreased HIV incidence in San Francisco and Vancouver.[19,20] Even in HPTN 052, however, with each partner in the serodiscordant relationships being carefully counseled and followed in the context of a rigorous clinical trial, more than one-fourth of all new infections were attributed to nonprimary partners.[21] These data underscore the importance of testing and serostatus disclosure if "treatment as prevention" is expected to yield maximal benefits.[22] Additionally, the benefits of public health approaches to lowering community viral load for disease prevention are based on the premise that the majority of persons with HIV infection can be identified, then linked to care, retained in care, and have their treatment initiated while they are asymptomatic, with optimal adherence to their therapeutic regimen. Unfortunately, recent data from a resource-rich environment—the United States—found that fewer than one-third of all Americans infected with HIV were virologically suppressed.[23] These findings suggest that, for antiretroviral agents to have a maximal impact on decreasing the transmission of new HIV infections, the expansion of HIV testing will be important. Although the approval of a home-use rapid HIV antibody test may be helpful for some, enhanced engagement of primary care providers in the United States and globally to identify the millions of people infected with HIV who are unaware of their status will be extremely important. For those who test negative, health care providers will have to be trained to assess their ongoing risks, and for those who are at greatest risk for seroconversion, PrEP may be useful.

In this new era of using antiretroviral therapy for HIV prevention, many questions remain. The data that have emerged over the past few years have generated new excitement that while awaiting the development of a highly protective HIV vaccine and/or a cure for people living with the disease, we now have the tools available that can significantly decrease the rate of new infections. The ultimate challenges for this strategy will be the implementation aspects—that is, how to get people to test, seek care, and become adherent to chronic medication regimens. Cost will also be an important factor to consider, but the cost of allowing 2 million new HIV infections to occur every year in the foreseeable future would be even more undesirable.

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EARLY ANTIRETROVIRAL THERAPY AND PREVENTION OF HIV-1 INFECTION IN SERODISCORDANT COUPLES

Cohen MS, Chen YQ, McCauley M, et al; HPTN 052 Study Team. **Prevention of HIV-1 infection with early antiretroviral therapy.** *N Engl J Med.* 2011; 365(6):493-505.
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The landmark HPTN 052 study was the first randomized, controlled trial to definitively show that earlier initiation of antiretroviral therapy in HIV-serodiscordant couples is associated with decreased disease transmission to the HIV-uninfected partner. The study enrolled 1763 couples, in which one of the partners was HIV-1-positive and the other partner was HIV-1-negative. In HPTN 052, HIV-infected partners had CD4 counts between 350 and 550 cells/mm3 at the time of study entry and a primary HIV-uninfected partner was enrolled. Of the 1763 couples evaluated, 278 were from the Americas (Brazil and the United States); 531 were from Asia (Thailand and India); and 954 were from Africa (Botswana, Kenya, Malawi, South Africa, and Zimbabwe). The couples were provided with condoms and received regular counseling.

The infected partners in the early-therapy group were offered state-of-the-art, three-drug antiretroviral therapy, whereas the HIV-infected persons in the delayed-therapy group were observed until they developed HIV-related symptoms and/or their CD4 counts dropped to < 250 cells/mm3. At the time of study termination, a total of 39 HIV-1 transmission events were reported—four in the early-therapy arm and 35 in the delayed-therapy arm—which was highly statistically significant ($P < .0001$). Additional laboratory analyses found that 11 of the 39 events were not linked—that is, the HIV-uninfected partners became infected with a viral isolate that suggested they had a relationship outside of their primary one. Among the 28 linked transmissions, only one transmission occurred in the early-therapy group and 27 in the delayed-therapy group ($P < .001$). In the one case in which an individual transmitted HIV while receiving antiretroviral therapy, molecular analysis found that this person had been on treatment for < 90 days at the time his partner became newly HIV-infected.

These data suggest that early initiation of antiretroviral therapy is extremely potent in decreasing HIV transmission, but in the one case in which transmission did occur in a patient receiving antiretroviral therapy, the data suggest that viral suppression must be well established before people are rendered less infectious.

During the study, risk-taking behavior decreased, as measured by self-reports as well as by decreases in the incidence of STIs. Clinical events were less common in the early-therapy arm than in the delayed-therapy arm, with 40 treatment end points (as measured by first serious HIV-1–related clinical event or death) occurring in the early-therapy group during the study vs 65 in the delayed-therapy group. The difference in incident events was most marked for extrapulmonary tuberculosis, with 17 participants developing this infection in the delayed-therapy arm, compared with three participants in the early-therapy arm ($P = .002$). These data are highly suggestive that early initiation of antiretroviral therapy can be associated with decreased HIV transmission among HIV-uninfected partners and improved clinical outcomes among HIV-infected partners.

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PRE-EXPOSURE ANTIRETROVIRAL CHEMOPROPHYLAXIS FOR HIV PREVENTION AMONG MEN OR TRANSGENDER WOMEN WHO HAVE SEX WITH MEN

Grant RM, Lama JR, Anderson PL, et al; iPrEx Study Team. **Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.** *N Engl J Med.* 2010; 363(27):2587-2599.

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The iPrEX study was designed to evaluate whether tenofovir plus emtricitabine as PrEP decreased HIV incidence among HIV-uninfected men and transgender women who have sex with men. The study randomized 2499 HIV-seronegative men or transgender women who have sex with men to daily tenofovir plus emtricitabine or to an identical placebo tablet. The majority of participants were recruited from Peru and Ecuador, with other sites in Brazil, the United States, South Africa, and Thailand. The iPrEx intervention involved a comprehensive prevention services package that included monthly HIV testing, risk-reduction counseling, free condoms, STI testing if any symptoms were present, and routine STI screening for all participants at least every 24 weeks, as well as partner treatment and PrEP, if requested, and hepatitis B vaccination at the onset of the study.

Half of the participants were < 25 years of age. The majority (72%) of the subjects were Hispanic, and 43% had completed college. After 144 weeks, 64 HIV infections were reported in the placebo arm vs 36 HIV infections among those who received tenofovir plus emtricitabine, representing a 44% reduction in HIV acquisition ($P = .005$). When examining the subgroups, observers found no difference in efficacy based on age, race/ethnicity, education, alcohol use, or circumcision status. Individuals who engaged in receptive anal intercourse, however, were more likely to be protected when treated with tenofovir plus emtricitabine. A subsequent analysis that evaluated whether tenofovir was present in the

blood of subjects before seroconversion found that of the 36 patients assigned to tenofovir plus emtricitabine who became HIV-infected, no drug was detected in the blood of 33 of them, and only three had any tenofovir detected in the active treatment group. When calculating the relative protection afforded by having tenofovir in the blood, the relative reduction in HIV risk with tenofovir plus emtricitabine was 92%. Younger subjects were less likely to have tenofovir detected in their blood, whereas individuals engaging in receptive anal intercourse were much more likely to have tenofovir detected.

No differences were observed in the prevalence of any adverse events or serious adverse events between the two treatment arms. Creatinine elevations were more common among those assigned to tenofovir plus emtricitabine compared with those assigned to placebo (28 events vs 15 events, respectively), but the difference was not statistically significant. Moreover, in all but one case in which an individual with an elevation in creatinine discontinued the drug, creatinine levels remained normal after restarting the medication. A small decrease (about 1%) in BMD of the spine was reported among persons treated with tenofovir plus emtricitabine, but it was not clinically significant and there was no increase in fractures or other osteopenia-related events among those assigned to tenofovir plus emtricitabine. A small number of patients (2%) who received tenofovir plus emtricitabine were more likely to experience nausea or unintentional weight loss in the first days of initiating therapy compared with those treated with placebo ($P = .04$). Among those in the tenofovir plus emtricitabine group, two developed an M184V mutation consistent with emtricitabine resistance, but no emerging tenofovir resistance was reported in the study.[1]

Reference

1. Grant, RM. 18th Conference on Retroviruses and Opportunistic Infections. Oral Abstract: Advances in PrEP. Scientific Overview: Pre-exposure Chemprophylaxis for Prevention of HIV among Trans-women and MSM: iPREx Study. March 1, 2011 Accessed February 25, 2013.

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ANTIRETROVIRAL PRE-EXPOSURE PROPHYLAXIS FOR HIV PREVENTION AMONG HETEROSEXUAL MEN AND WOMEN

Baeten JM, Donnell D, Ndase P, et al; **Partners PrEP Study Team. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women.** *N Engl J Med.* 2012; 367(5):399-410.

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The Partners PrEP Study enrolled 4758 HIV-serodiscordant, heterosexual couples from Kenya and Uganda. At the time the study was conducted, the CD4 counts of HIV-infected partners were sufficiently high that according to national guidelines, antiretroviral therapy was not warranted. The HIV-uninfected partners were randomized to one of three treatment regimens: (1) once-daily tenofovir alone, (2) once-daily combination tenofovir plus emtricitabine, or (3) an identical-looking placebo. All couples received ongoing prevention counseling and were provided free condoms and contraceptive services. HIV incidence was 1.99 per 100 person-years in the placebo group, 0.65 in the tenofovir-alone group, and 0.50 in the tenofovir-plus-emtricitabine group, translating into a 67% reduction in HIV incidence in the tenofovir-only group and a 75% decrease in the tenofovir-plus-emtricitabine group. Both of these differences were highly statistically significant ($P < .001$) in each active treatment group compared with placebo, but did not differ significantly from each other.

Adherence was excellent in the study, estimated to be 97% based on self-reports and pill counts. When drug levels were measured, tenofovir was detected > 80% of the time in blood specimens of study participants assigned to active treatment. Tenofovir and emtricitabine were well tolerated, with mild diarrhea being more common in the active treatment arms but not associated with study drug discontinuation. No differences in renal function were reported among the study groups. When comparing drug levels among

those assigned to active treatment who became infected with HIV and those who did not, having tenofovir detected in the blood was associated with a 90% decreased risk for HIV in the tenofovir-plus-emtricitabine group and an 86% risk reduction in the tenofovir-only group. There was no evidence of risk compensation among study participants.

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PREEXPOSURE PROPHYLAXIS WITH ANTIRETROVIRAL THERAPY AND REDUCTION IN HETEROSEXUAL HIV TRANSMISSION IN BOTSWANA

Thigpen MC, Kebaabetswe PM, Paxton LA, et al; TDF2 Study Group. **Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana.** *N Engl J Med.* 2012; 367(5):423-434.

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The tenofovir disoproxil fumarate-2 (TDF-2) study, conducted by the US Centers for Disease Control and Prevention, enrolled 1219 young, high-risk, uninfected heterosexuals in Botswana who were randomized to once-daily oral tenofovir plus emtricitabine vs placebo. The overall protective efficacy was 62.2% (95% confidence interval, 21.5 to 83.4; $P = .03$). High rates of adherence were reported among study participants, with tenofovir detected in 79% of the blood specimens of those enrolled in the active treatment arm. The incidence of side effects was low, with < 5% of the participants reporting nausea or diarrhea[1]—the most common side effects in the tenofovir-plus-emtricitabine arm—which did not differ significantly from that in the placebo arm. Nearly half (45%) of the participants were women and 94% were single.

Although the study sample size was not sufficiently large to make comparisons between genders, trends suggested that both men and women benefited from chemoprophylaxis. Among the participants who were assigned to the tenofovir-plus-emtricitabine arm and became HIV-infected, transmitted viral resistance was rare, although two participants had an M184V mutation detected at their first seroconversion visit and one had a K65R mutation. Because sexual partners were not routinely enrolled in the study, it cannot be known for certain whether these participants were infected with a drug-resistant virus, or whether they were infected with a wild-type virus and resistance evolved in the setting of inadequate virologic suppression.

Reference

1. Horn, Tim. PrEP Cuts Sexual HIV Transmissions 62% to 78% in Men and Women. AIDSMEDS. 2011.

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PREEXPOSURE PROPHYLAXIS WITH ANTIRETROVIRAL AGENTS FOR PREVENTION OF HIV INFECTION AMONG AFRICAN WOMEN

Van Damme L, Corneli A, Ahmed K, et al; FEM-PrEP Study Group. **Preexposure prophylaxis for HIV infection among African women.** *N Engl J Med.* 2012; 367(5):411-422.

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The FEM-PrEP study enrolled 2120 high-risk young women in Tanzania, Kenya, and South Africa. Participants received risk reduction counseling and were randomized to daily tenofovir plus emtricitabine or placebo. Overall, 59% of the women were < 25 years of age. Only about half of the women reported regular condom use. The participants averaged 3.7

vaginal sex acts per week, with the maximum number at 28 acts per week, suggesting that some of the women were engaging in transactional sex. At baseline, 14.0% of the women had vaginal chlamydial infection and 5.7% had gonorrhea.

HIV incidence was 4.7% per 100 person-years in the tenofovir-plus-emtricitabine group and 5.0% in the placebo group, resulting in a 6% decrease in HIV incidence, which was not statistically significant (*P*= .81). Medication adherence was low among the women, with only 26% of those assigned to the active treatment arm having tenofovir-emtricitabine detected in their blood. Ironically, 70% of the women reported that they thought they were at low risk for acquiring HIV, despite reporting many sexual partners and having STIs diagnosed at baseline. Participants also overestimated their adherence, with 95% reporting usually/always taking pills; adherence levels of 86% to 89% were based on pill counts. Drug levels of the medication suggested that the women were overestimating their level of adherence, however, because of either social desirability bias or because they may have received benefits from the study (compensation and/or medical care and referrals) that they feared would be withdrawn if they fully disclosed their level of nonadherence. The medication was well tolerated, with no relationship demonstrated between the low level of side effects (primarily transient nausea or changes in bowel habits) and medication nonadherence.

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