Evaluating Outcomes of the President’s Emergency Plan for AIDS Relief in Africa

TO THE EDITOR: I applaud Bendavid and Bhattacharya (1) for undertaking a much-needed quantitative evaluation of the effectiveness of the President’s Emergency Plan for AIDS Relief (PEPFAR), the largest international health initiative dedicated to a single disease.

Although it is important to recognize PEPFAR’s success in decreasing AIDS-related deaths by more than 10% and in providing antiretroviral therapy to more than 2 million people (2), it is no less important for the authors to conclude that PEPFAR has had no success in lowering HIV prevalence in adults. In 2007, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that there were 2.7 million new HIV infections, which is 5 new infections for every 2 persons receiving treatment (3).

As a woman living with HIV in one of the hardest-hit countries, Botswana, I urge the world to recognize that a meaningful, sustainable response to the pandemic must focus on HIV prevention and on women, particularly young women. Most persons living with HIV/AIDS live in sub-Saharan Africa (22 million of the 33.2 million worldwide) and are adults, of which 61% are women (3). In my region, 3 young women aged 15 to 24 years are infected for every young man in the same age range (4).

To be most effective, PEPFAR-supported prevention programs must ensure that all persons have access to the full range of information and services to protect themselves from HIV throughout their lives, including female and male condoms. PEPFAR’s effectiveness also requires integration of family planning and other HIV services; widespread access to comprehensive sexual education; and the protection of all persons’ human rights to live free of stigma, discrimination, and violence. Recipients of PEPFAR funding must be free to work with all communities at risk for HIV, including sex workers.

It is our moral obligation and fiscal responsibility to use PEPFAR funding to prevent as many infections as possible. Large sums of money spent unwisely will not save lives and will create an ever-growing need for increased resources in the future.

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Potential Conflicts of Interest: None disclosed.

References

TO THE EDITOR: Bendavid and Bhattacharya (1) reported on PEPFAR and its positive effects on HIV-related prevalence and AIDS mortality in certain sub-Saharan African countries since its implementation in 2003. The authors compared trends in HIV prevalence (reported as the number of persons living with HIV infection) and AIDS mortality (reported as number of deaths) before and after the initiation of PEPFAR activities in 12 focus countries and 29 control countries that had a generalized HIV epidemic in 1997 to 2002 and 2004 to 2007. On the basis of 4 years of PEPFAR activity, AIDS mortality from 2004 to 2007 decreased the most in focus countries compared with control countries (10.5 percentage points lower; P = 0.001), and prevalence trends did not differ between groups (1.7 percentage points lower; P = 0.124).

On the basis of these results, we hypothesized that PEPFAR activities would also be associated with decreased HIV incidence in focus countries. To test this hypothesis, we obtained raw prevalence data and AIDS and non-AIDS mortality data for adults and children from 1997 to 2006 from UNAIDS (2) and the U.S. Census Bureau (3) and population estimates from 1997 to 2006 from the U.S. Census Bureau (4). We used the following formula to estimate HIV incidence in each of the 41 countries from 1997 to 2006:

\[
\text{Incidence} (t_0, t_1) = \frac{\text{Prevalence} (t_1) - \text{Prevalence} (t_0) + \text{AIDS Deaths} (t_0, t_1)}{\text{Non-AIDS Deaths} (t_0, t_1) - \text{AIDS Deaths} (t_0, t_1)} - A
\]

In brief, \( t_0 \) is the beginning of the time interval, and \( t_1 \) is the end of the time interval, for \( t_0, t_1 = 1997, \ldots, 2007 \); with \( t_0 < t_1 \). Note that by using the formula (A), we were only able to estimate HIV incidence from 1997 to 2006.

Appendix Figures 1 and 2 (available at www.annals.org) show HIV incidence from 1997 to 2006 by control countries and focus countries, respectively. A general trend is toward lower HIV incidence rates, with notable exceptions, including Lesotho, Sudan, Swaziland, and Togo among the control countries, and Kenya, Mozambique, Namibia, and Zambia among the focus countries. Overall, 28% (8 of 29) of the control countries and 50% (6 of 12) of the focus countries had decreased incidence from 2003 to 2006. Finally, the median percentage change in HIV incidence rate between 2003 and 2006 was 1.76 percentage points (interquartile range [IQR], −0.20 to 3.35 percentage points) for control countries and 0.96 percentage points (IQR, −2.41 to 23.56 percentage points) for focus countries.

Several authors (5, 6) have recently postulated that expanded antiretroviral therapy coverage may play an important role in curbing the global spread of HIV. Our incidence estimates for focus and control countries are compatible with the postulated beneficial effect of treatment on the prevention of HIV transmission. However, caution should be exerted when using this ecological approach to evaluate these results, because the selection of focus and control countries was not random. PEPFAR comprises a number of activities not limited to the introduction of antiretroviral therapy, and PEPFAR is part of a complex national response. Therefore, given the breadth of PEPFAR-supported activities and the complex nature of the country-level response, further research and careful prospective monitoring of the relative contribution of interventions, such as expanded antiretroviral therapy, to the growth of the HIV epidemic is needed. Because of the current economic climate, scientific evidence regarding the relative effect of public health interventions is critical to inform public policy in attempts to control the spread of HIV.
Letters

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Potential Conflicts of Interest: Grants received: J.S.G. Montaner (Abbott, Argos Therapeutics, Bioject, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Hoffmann-La Roche, Janssen-Ortho, Merck Frost, Panacos, Pfizer, Schering, Serono, Therapeutics, Tibotec [Johnson & Johnson], Trimeris).

References

TO THE EDITOR: Bendavid and Bhattacharya (1) present an interesting and innovative approach to analyzing the effect of PEPFAR in focus countries. We would like to provide some additional information on the scope of PEPFAR activities and further elaborate on some conclusions and interpretations discussed in the article.

Since 2007, the U.S. Census Bureau has evaluated PEPFAR through estimations of life-years gained, not deaths averted, at the recommendation of UNAIDS (2). The Bureau (3) estimates that 3.2 million cumulative life-years were gained from 2004 to 2009 in the 15 PEPFAR focus countries. The authors’ conclusion that no difference in the relative change in prevalence exists between focus and nonfocus countries is a bit misleading. Although they find that PEPFAR has had an effect on mortality, they do not account for this in their analysis of prevalence, with the exception of a brief comment in the Discussion section. In fact, for a given incidence level, a reduction in mortality due to antiretroviral therapy should result in an increase in prevalence (or less of a decrease) in focus countries; therefore, the finding of decreased mortality and a stable prevalence suggests a possible decrease in incidence in the PEPFAR focus countries.

The authors tried to adjust their models for other sources of HIV funding by using the amount of funding from the Global Fund. However, this does not adequately account for overall per capita HIV funding from all other sources, including PEPFAR, other parts of the U.S. government, and other donors who have put considerable resources into some of the nonfocus countries. These contributions may diminish or mask the perceived effect of PEPFAR spending in focus countries versus nonfocus countries.

We appreciate the authors’ efforts to better understand and quantify the effect of PEPFAR. Their belief that no evaluations have been done to date suggests that the U.S. government needs to be more proactive in disseminating and publicizing the evaluations that have in fact been done, especially in the peer-reviewed scientific literature. We also encourage others to develop methods for measuring the success of PEPFAR and other efforts to mitigate the effect of the HIV epidemic worldwide.

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Potential Conflicts of Interest: None disclosed.

References

IN RESPONSE: We thank Ms. Sedio, Dr. Montaner and colleagues, and Dr. Johnson and colleagues for their thoughtful comments. Ms. Sedio points out the importance of HIV prevention as a cornerstone of long-term response to the epidemic. We agree, but need to highlight 2 important caveats: First, our analysis does not suggest that PEPFAR failed on prevention. As Drs. Montaner and Johnson and their colleagues suggest, a relative reduction in deaths with parallel prevalence trends implies some reduction in incidence.

Second, although we are in favor of HIV prevention, it is not clear which prevention efforts are effective and sustainable. Measuring incidence directly would greatly help in evaluating prevention programs and in resource-allocation decisions. Dr. Montaner and colleagues tested the hypothesis that PEPFAR activities were associated with decreased HIV incidence and found a lower median percentage decrease in incidence in the focus countries. This is a first-pass analysis, which calls into question whether PEPFAR was associated with a decrease in HIV incidence. We agree with their call to define the relative contribution of interventions on the course of the epidemic, especially as the specter of decreasing resources looms over PEPFAR.
Finally, Dr. Johnson and colleagues point to an evaluation of PEPFAR done by the U.S. Census Bureau, of which we were not aware when we performed our work. We applaud the U.S. Census Bureau for estimating PEPFAR’s effect on health outcomes in terms of life-years gained. We can transform our estimates to life-years gained by estimating the number of deaths averted each year assuming a 10% reduction in mortality associated with PEPFAR, and calculating the life-years gained given the number of deaths averted each year. Thus, we estimate that PEPFAR was associated with approximately 260,000 deaths averted in 2004, 284,000 in 2005, 313,000 in 2006, and 344,000 in 2007. Adding up the life-years gained (260,000 × 4 + 284,000 × 3 + 313,000 × 2 + 344,000 × 1), we arrive at an estimate of 2.9 million life-years gained from 2004 to 2007, which is in good agreement with the U.S. Census Bureau’s estimates.

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Potential Conflicts of Interest: None disclosed.

Hormone Therapy Suspension and Mammography in Women’s Health Initiative Clinical Trials

TO THE EDITOR: The findings of Buist and colleagues (1) are addressed and expanded on by those of the WHI (Women’s Health Initiative). In the WHI clinical trial evaluating estrogen plus progestin (2), 16,608 postmenopausal women were randomly assigned to combined hormone therapy or placebo. When the trial intervention was ended, women were informed by letter to stop taking study pills that day. Almost all did. Women in the combined estrogen plus progesterin group had significantly more mammograms that required a physician-directed intervention (those in which short-interval follow-up was suggested, those with suspicious abnormalities, and those highly suggestive of malignant conditions) during the intervention (2) and throughout the first postintervention year but not thereafter (P = 0.005) (3). Thus, somewhat more than 1 year is required for improvement in mammography performance after stopping combined estrogen plus progesterin use.

In an ancillary study in the same WHI clinical trial (4), the association between combined estrogen plus progesterin use and mammographic density was examined. In this randomly identified subsample of 1413 postmenopausal women, a statistically significant 6.0% increase was found in density after 1 year, and a 4.9% increase was found at 2 years with estrogen plus progesterin use (4). The magnitude of the increase in breast density was somewhat higher than that cited in the PEPI (Postmenopausal Estrogen/Progestin Interventions) trial. Taken together, the PEPI and WHI findings suggest that changes in breast density associated with combined hormone therapy use are substantially greater in magnitude than those observed during a menstrual cycle.

Finally, in the WHI randomized clinical trial evaluating estrogen alone in postmenopausal women with previous hysterectomy (n = 10,739) (5), mammograms that were suspicious or highly suggestive of malignant conditions were not more common in the estrogen-alone hormone groups, unlike in the WHI trial of combined hormone therapy, in which an increase in abnormal mammograms was seen in women receiving estrogen plus progesterin (2). Thus, differences in mammography recall rates between women receiving estrogen alone versus combined estrogen plus progestin would be anticipated. Awareness of these findings from the WHI randomized trials should put those of Buist and colleagues in a more complete clinical context.

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References

Red Yeast Rice for Dyslipidemia in Statin-Intolerant Patients

TO THE EDITOR: We read with interest the article by Becker and colleagues (1). The emergence of red yeast rice as a dietary supplement and cholesterol-lowering agent shows why such supplements are currently classified as unapproved drugs under the Dietary Supplement Health and Education Act (2).

Red yeast rice as a supplement did not exist until 1993. However, it has been used as a food coloring and flavoring agent throughout the Orient for centuries, and its medicinal use for indigestion, diarrhea, and blood circulation is mentioned in ancient Chinese pharmacopoeia. Originally, it was made by fermenting cooked white rice with Monascus purpureus in the open air. In November 1978, Dr. Alberts (Merck, Whitehouse Station, New Jersey) isolated lovastatin from Monascus purpureus. In February 1979, Professor Endo (Tokyo Noko University, Tokyo, Japan) also isolated monacolin K, a lovastatin analogue, from a certain strain of M. purpureus. In 1987, the U.S. Food and Drug Administration (FDA) approved lovastatin as the first cholesterol-lowering drug (3). The first red yeast rice supplement, Cholestin, was made by Pharmanex (Provo, Utah) in 1993. It was advertised as a natural, ancient Chinese remedy that...
lowered cholesterol levels. Trials (4, 5) showed short-term effectiveness and safety.

Subsequent FDA investigation showed that this supplement contained substantial quantities of lovastatin. This was attributed to the use of proprietary technology and of a particular strain of *Monascus purpureus* to ferment rice for manufacturing the supplement. When samples of traditional red yeast rice from Chinese stores were tested, most contained little or no lovastatin (6). As a result, the FDA declared Cholestin an unapproved drug rather than a supplement and banned it from the market in 2001 (2). In addition, statin-related toxicity from red yeast supplements was reported (7–12). Although all red yeast rice supplements containing lovastatin were withdrawn from the market by 2008, they are still available in other countries and via the Internet.

In summary, red yeast rice supplements containing lovastatin are considered unapproved drugs by the FDA. Therefore, any trials using them are immaterial and perpetuate their mystification.

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Potential Conflicts of Interest: None disclosed.

References

TO THE EDITOR: Becker and colleagues (1) conclude that red yeast rice might be a treatment option in persons who cannot tolerate statins. The trial studied persons who had previously discontinued statins secondary to myalgia but excluded persons with the more-serious diagnosis of myositis or rhabdomyolysis.

The authors indicate that the daily dose of red yeast rice is equivalent to only 6 mg of lovastatin and is much lower (and presumably safer) than the recommended daily dose of lovastatin tablets, which is 20 to 40 mg. The active component of lovastatin is its metabolite, lovastatin hydroxyacid. The only pharmacokinetic study of red yeast rice compared it with 20-mg lovastatin tablets (2). This study was unfortunately confounded by co-administration of grapefruit juice. However, the maximum concentration (4.31 vs. 4.55 ng/mL, red yeast rice vs. lovastatin, 20 mg, respectively) and area under the curve (29.47 vs. 31.63 ng/mL per hour) for lovastatin hydroxyacid after red yeast rice were similar to those of another study (3) in which lovastatin, 80 mg, was administered without grapefruit juice. Furthermore, red yeast rice contains many substances other than lovastatin, including sapogensins; citrinin; and various colored polyketide pigments, which are potential inhibitors of CYP3A4 and P glycoprotein. Therefore, the oral dose of lovastatin in red yeast rice may not reflect the subsequent blood concentrations of lovastatin or its active metabolite after administration. Until appropriate pharmacokinetic studies of red yeast rice are performed (that is, without confounding co-administration of grapefruit juice), this issue is unresolved.

Red yeast rice is a sweet-smelling substance; therefore, participants may have been unblinded unless the placebo had a similar odor. This is important because the key outcome of myalgia is subjective. Of note, the increase in creatinine phosphokinase was slightly greater in the treatment group than in the placebo group, and the change almost reached statistical significance at 12 weeks (*P = 0.057*). Because the treatment group comprised only 30 persons, the statistical power to differentiate any effect was small. Muscle injury with red yeast rice is a concern because several recent cases of myopathy have been reported (4), including a series of 4 cases (5).

Given these issues, considerable caution is necessary before recommending red yeast rice to persons who cannot tolerate statins. However, the conclusions regarding the concomitant lifestyle program are very welcome and highly applicable.

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Potential Conflicts of Interest: None disclosed.

References
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Potential Conflicts of Interest: None disclosed.

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TO THE EDITOR: We read with interest the article by Becker and colleagues (1) on the effects of red yeast rice in statin-intolerant patients. The results are certainly interesting, but the safety profile of red yeast rice when used in the “real world” should not be underestimated.

We recently conducted an analysis (2) in the Italian adverse drug reactions database of natural health products (including herbal drugs and food supplements) and found 4 cases of myopathy associated with red yeast rice (dose range, 200 to 1200 mg/d; data were not available on monacolin content). Each patient reported muscle pain, and creatinine phosphokinase levels were increased, ranging from 288 to 401 IU/L. The time to onset was 2 to 6 months (6 months in 1 statin-intolerant person). After product withdrawal, 3 persons achieved complete recovery, whereas 1 statin-intolerant patient had persistently increased creatinine phosphokinase levels for several months.

Although these cases of myopathy cannot be considered conclusive in defining the safety profile of red yeast rice, neither can the trial by Becker and colleagues. In fact, the design of clinical trials typically renders them unsuitable to define drug safety—definition of drug safety is usually left to postmarketing surveillance. The number of participants enrolled in Becker and colleagues’ trial is low (n = 62), and although that number is probably adequate to define the proposed efficacy outcomes, it certainly is inadequate to obtain clinically significant information on safety.

The fact that all patients were statin intolerant could increase the sensitivity of the study, with a myalgia recurrence rate (7%) lower than that expected in patients challenged with a second statin (57%). Although this could support the hypothesis that recurrence rates of myalgia are lower in statin-intolerant patients exposed to red yeast rice than in those exposed to a different statin (no direct comparison was conducted in this sense with appropriate statistical analyses), we strongly believe that physicians should still be cautious to avoid overestimating this product’s safety.

The wide availability of red yeast rice as a food supplement (containing many pharmacologically active molecules, such as monacolin K and congeners) could in fact lead statin-intolerant patients to use this product without any medical advice, exposing them to an increased risk for myopathy. This is exactly what happened in the 4 Italian patients we reported (2), who underestimated the risk for myalgia, myopathy, and rhabdomyolysis of red yeast rice. They considered red yeast rice to be a “natural” lipid-lowering product, a food supplement, and therefore absolutely safe.

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References
Other side effects include anxiety, insomnia, and dizziness. Less upset, diarrhea, loss of appetite, nausea, vomiting, and headache.

Bacteroides fragilis exceptions include galactorrhea. Cefpodoxime proxetil may cause stomach pain.

Case Report: A 40-year-old, ambulatory woman reported passage of milk from both breasts for 2 days. She had been taking cefpodoxime, 200 mg twice daily for 4 days, to treat fever and cough. She was not taking any of the drugs or herbs known to cause galactorrhea. She reported no sexual activity in the past 10 days. She reported no vision disturbance or symptoms of increased intracranial pressure. A physical examination revealed no other abnormality. Her fever and cough resolved, but she continued to have galactorrhea. A serum pregnancy test result was negative, and renal function test results and thyroid-stimulating hormone levels were normal. Her serum prolactin concentration was 6854.7 pmol/L (reference values for nonmenopausal women, 625 to 4028.1 pmol/L). A brain magnetic resonance image was normal. Cefpodoxime therapy was started. Seven days later, when her serum prolactin level was 1111.2 pmol/L, the breast discharge stopped. One month later, her serum prolactin level decreased even further to 777.84 pmol/L.

Discussion: Galactorrhea is the nonpuerperal secretion of milk, which can be confirmed if necessary by visualizing fat droplets in breast secretions by using low-power microscopy. Many drugs cause galactorrhea through antidopaminergic effects, including antipsychotic drugs, metoclopramide, and domperidone (1)—as many as 15% of women report galactorrhea within 7 to 75 days after starting antipsychotic drugs (2).

Cefpodoxime proxetil is an orally administered, extended-spectrum, semisynthetic antibiotic of the cephalosporin class. It is active against most gram-positive and -negative organisms. Notable exceptions include Pseudomonas aeruginosa, Enterococcus species, and Bacteroides fragilis. It is commonly used to treat acute otitis media, pharyngitis, and sinusitis. Cefpodoxime proxetil may cause stomach upset, diarrhea, loss of appetite, nausea, vomiting, and headache. Other side effects include anxiety, insomnia, and dizziness. Less common side effects include fever, easy bleeding or bruising, change in quantity of urine, and seizures. Allergic reactions include difficulty breathing, rash, hives, and itching.

To the best of our knowledge, this is the first report of galactorrhea with cefpodoxime-associated hyperprolactinemia (3). We determined that the sequence of events starting with cefpodoxime treatment, then galactorrhea, and then the disappearance of galactorrhea after discontinuing cefpodoxime corresponds to a score of 6 on the Naranjo nomogram (4), which indicates cefpodoxime probably caused the galactorrhea. We believe that the mechanism involved elevated serum prolactin levels during cefpodoxime use because the serum prolactin level decreased after stopping cefpodoxime therapy.

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Potential Conflicts of Interest: None disclosed.

References

CORRECTIONS

Correction: Principal Investigators for Mammography Schedule Models

In the recent article on model estimates of potential benefits and harms of mammography screening under different schedules (1), 2 principal investigators of the modeling teams were omitted from the footnote on page 738. Dr. Lee was the principal investigator for the Dana-Farber Cancer Institute model, and Dr. de Koning was the principal investigator for the Erasmus University model. This has been corrected in the online version.

Reference

Correction: Evidence-Based Breast Cancer Prevention

In the recent editorial on evidence-based breast cancer prevention (1), there is an error in the fifth paragraph. The second sentence says “Mandelblatt and colleagues report that in all 6 models, biennial screening of women aged 50 to 69 years averts 70% to 90% of breast cancer deaths attainable with mammography screening.” It should say “70% to 99%.” This has been corrected in the online version.

Reference