Aspirin Is Indicated for Primary Prevention of Cardiovascular Events in HIV-Infected Patients

To the Editors:

The recommendations on aspirin use for the primary prevention of cardiovascular events,[1] based on cardiovascular risk (CVR) calculation according to the Framingham scale, have recently been published.[2] Despite the growing interest in CVR among HIV-infected patients,[3,4] the use of aspirin in these subjects has received scant attention to date. However, the gradual aging of these patients means that we are reaching a point where aspirin for primary prevention may be indicated according to the above-mentioned recommendations. We have reviewed the indication of aspirin in a group of HIV-infected patients based on the criteria of these recommendations, with calculation of CVR using the Framingham tables.

A total of 120 consecutive HIV-infected adults were included in a cross-sectional observational study. Demographic data were recorded, along with information on smoking or diabetes, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and blood glucose. Blood pressure was recorded after the consensus recommendations, with confirmation of the new diagnoses based on Holter blood pressure monitoring to rule out white-coat hypertension. The Framingham tables were used to calculate CVR. The indication of aspirin was based on the published criteria for males >45 years of age and females >55 years of age. Calculation was also made of the variation in percentage indication over the coming years as the patients gradually exceed this age limit without changes in the risk factors. In our experience, primary prevention with aspirin would be indicated in 30.8% of the patients, according to the assessment of the Framingham study, yet only 2 patients were taking the medication. Among the males, the percentage would reach 40%. Without modification of the CVR factors, over the next 5 years the indication would be expanded to another 15% as a result of the aging of the group.

Therefore, application of the recently published recommendations on the use of aspirin in HIV-infected patients could help reduce the rise in cardiovascular events described in some studies. Aspirin would be indicated in a large proportion of patients, particularly in males, and this indication moreover may be expected to increase over the coming years.

In the management of CVR among HIV-infected patients, it is therefore necessary to also consider aspirin as primary prevention treatment.

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Evaluation of the Safety of Nevirapine Therapy During Pregnancy

To the Editors:

Nevirapine (NVP) has been used worldwide as part of an effective antiretroviral regimen in both pregnant and nonpregnant women. In most cases, NVP is well tolerated, but in some cases, NVP-associated rash and hepatitis have been life threatening, particularly in women.[1,2] Although NVP has been extensively studied in pregnancy and is highly effective in reducing HIV transmission to the fetus,[3] its safety during pregnancy has been questioned.[4] In our clinics, we anecdotally noted that women who initiated NVP during pregnancy were less likely to have adverse events (AEs) to NVP than those who were not pregnant. The purpose of this study was to determine whether pregnant women have a decreased risk of rash or hepatitis (AEs) compared with nonpregnant women who take NVP.

Institutional Review Board approval was obtained to conduct a retrospective cohort study of women more than the age of 13 with HIV who received NVP as part of an outpatient antiretroviral regimen at Kaiser Permanente of the Mid-Atlantic States between January 1995 and May 2007. Women were eligible for study if they continued on NVP for 30 days (unless NVP was stopped before 30 days for an AE) and had at least 1 documented follow-up visit 30 days after NVP start. Women with congenital HIV infection, who started NVP outside KP, who took NVP for <30 days, or for whom there was no follow-up after NVP initiation were excluded. The primary outcome of interest was the occurrence of any grade rash or hepatitis within 90 days of NVP start. All rashes within the first 90 days were attributed to NVP. AEs were graded according to the AIDS Clinical Trials Group (ACTG) Scale,[5] with severe rash defined as grades 3 or 4. Hepatitis (both alanine aminotransferase and aspartate aminotransferase) was graded according to the Division of AIDS (DAIDS) AE grading system with severe hepatitis also defined as grade 3 or 4. Patients were defined as receiving opportunistic infection prophylaxis if they received prophylaxis for *Pneumocystis jeroveci* pneumonia or *Mycobacterium avium*. Women were defined as receiving contraceptive hormones if they used medroxyprogesterone (Depo-Provera) or oral contraceptives. Data were entered into a Microsoft Access database.

A total of 253 women, 42 pregnant (16.6%) and 211 nonpregnant (83.4%) were eligible for study. At baseline, the pregnant women were younger (mean

age 29.3 vs. 39.1 years, $P < 0.001$) and had higher CD4 counts (mean 406 vs. 330 cells/uL, $P = 0.003$), so were therefore less likely to require opportunistic infection prophylaxis ($P = 0.003$). There were no significant differences between the pregnant and nonpregnant women for race, viral load, or infection with Hepatitis B or C or syphilis.

Two pregnant (4.8%) and 43 nonpregnant women (20.4%) developed either rash or hepatitis after starting NVP [rate ratio = 0.234 pregnant vs. nonpregnant women, 95% confidence interval (CI): 0.0516 to 0.797, $P = 0.016$]. The number of days from NVP start to the AE for the 2 pregnant women was 42 and 54 days. One woman developed a grade 1 rash, the other a grade 2 hepatitis; both AEs resolved upon discontinuation of NVP. The time to AE onset could not be determined for 1 of the 42 nonpregnant women. Of the 41 with a known onset date, the AE for 31 occurred within the first 30 days, for 8 within days 31–60, and at day 408 and 487 for the remaining 2. The 2 women with time to AE >90 days both had hepatitis; 1 also had lactic acidosis. Both women normalized their transaminases upon discontinuation of the medication.

Mild to moderate AEs (grades 1–2) were seen in both pregnant women (4.8%) and 27 (12.8%) of the 211 nonpregnant women (RR = 0.372, 95% CI: 0.0782 to 1.308, $P = 0.140$). Serious AEs (grades 3–4) were seen in none of the pregnant and 16 (7.6%) nonpregnant women (RR = 0.0, 95% CI: 0.0 to 1.211, $P = 0.066$). Two of the nonpregnant women had both rash and hepatitis; 1 had both grade 3 rash and hepatitis, the other had grade 1 rash and grade 2 hepatitis. None of the women in our cohort developed fulminant hepatic failure or died.

In looking for other factors that may have contributed to the development of an AE, we found no significant interaction between baseline CD4 cell count, age, or the use of sulfa medications and the likelihood of developing either rash or hepatitis (data not shown).

All women were taking other medications with NVP; the most frequently occurring combination of drugs for all women was zidovudine/lamivudine (given as Combivir). The odds ratios, P values, and 95% confidence intervals for Combivir is shown in Table 1; the results for the other antiretroviral drugs (which were not significant) are not shown. Due to the zero frequency for AEs in pregnant women taking lamivudine, any AE odds ratio involving lamivudine and pregnancy or Combivir and pregnancy was estimated using logistic regression; the resulting estimated odds ratios are significant: $P = 0.001$ for lamivudine and $P = 0.002$ for Combivir. These results suggest that the likelihood of rash or hepatitis is very low for women administered either NVP and lamivudine or NVP and Combivir during pregnancy.

In this study, we report our finding that NVP toxicity is less likely to occur if it is initiated during pregnancy. Although our cohort of nonpregnant women has a similar rate of rash and hepatitis to other published cohorts of women who have used this drug,[1,6] our finding that NVP toxicity is less likely to occur in women who initiate NVP while pregnant is the first study that shows an association with pregnancy. A marker predictive of hypersensitivity is not yet available for NVP. In one study lead-in dosing of NVP 200 mg a day for 2 weeks followed by escalating to 200 mg twice a day reduced the risk of rash.[7] Although this dosing strategy is standard of care and is recommended in the package insert, it does not eliminate the risk of rash. The women in our study received the dose escalation as recommended, yet, we still noted a 20% rate of rash and/or hepatitis among our nonpregnant women. The package insert for NVP also states that when initiating NVP in combination with other antiretrovirals, female gender (including pregnant women), and CD4 >250 cells per cubic millimeter are associated with the greatest risk of hepatotoxicity.

Although we also identified the combination of zidovudine and lamivudine as possibly protective against AEs in pregnant women initiating NVP, this association has not been noted in other cohorts. In an Irish study of pregnant women, 2 women with CD4 counts over 400 cells per microliter who initiated NVP during pregnancy with Combivir developed fulminant hepatic failure and death.[4] According to that report, women were started on NVP well into their third trimester, although the women in our cohort were started, in most cases, either in the first trimester or early in the second trimester. A study by Hitti et al[8] compared the safety of NVP to nelfinavir when initiated during pregnancy.[8] The women in this study were started on 1 of these 2 drugs in combination with zidovudine plus lamivudine. This study was stopped early due to greater than expected toxicity and because of changes to the NVP prescribing information that recommended caution for women with CD4 cell counts greater than 250 cells per microliter. The women in the Hitti study who developed AEs all had CD4 counts well over 300 cells per microliter;

TABLE 1. Pregnancy Status and the Use of Specific Antiretrovirals and Estimates of Adverse Event Odds Ratios

Pregnancy and Status of Certain Antiretrovirals		Any Adverse Event		Adverse Event Rate (%)	Adverse Event Odds Ratio	Significance	Exact 95% CI
		Yes	No				
Lamivudine	Pregnant	0	33	0	0.0719	0.001	0 to 0.4273
	Not pregnant	27	89	23			
No lamivudine	Pregnant	2	7	22	1.406	0.970	0.1310 to 8.362
	Not pregnant	16	79	17			
Zidovudine and lamivudine combined	Pregnant	0	30	0	0.0729	0.002	0 to 0.4452
	Not pregnant	20	60	25			
No zidovudine and/or no lamivudine	Pregnant	2	10	17	0.9395	1.000	0.0941 to 4.860
	Not pregnant	23	108	18			
	Pregnant	2	40	5	0.1953	0.017	0.0221 to 0.8099
	Not pregnant	43	168	20			

they also all started NVP well into their second trimesters.

In another study, Natarajan et al[6] reviewed the safety of NVP in 175 women who initiated therapy while pregnant. As in our study, they found a lower than expected rash rate in their pregnant women (6.4% in their cohort compared with 4.8% in our cohort). However, their rash rate also included the women who began NVP therapy before becoming pregnant. For the women who initiated NVP during pregnancy, 10 women developed rash that was attributed to NVP; for these women the authors do not report the time during gestation at which NVP was started. Eight women in their cohort also developed hepatotoxicity; all women with hepatitis initiated NVP at 21 weeks gestation (late second trimester) or later.

Although large studies of NVP have shown the drug to be safe and effective when given as a single 200-mg dose during labor and delivery to prevent mother-to-child transmission of HIV,[3] initiation of continuous NVP-based therapy either in late in the second trimester or third trimester may be associated with increased risk of maternal toxicity.[9] Based on the findings in our cohort, timing of NVP initiation during pregnancy seems to be an important predictor of who will and will not develop an AE. Perhaps initiating NVP therapy during the first trimester or very early in the second trimester is protective against both rash and hepatitis.

NVP remains one of the most readily available and effective drugs to treat HIV infection and continues to be used worldwide, especially during pregnancy. Our results suggest that with careful monitoring for rash and hepatotoxicity, NVP in combination with lamivudine with or without zidovudine is safe to use in women, particularly pregnant women. CD4 guidelines should be adhered to despite the lack of such an association in our cohort. In the situation where a woman is considering pregnancy or becomes pregnant, our results support that it may be safe to initiate a regimen that contains NVP.

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The Coughing Patient: TB or Not TB; That Is The Question

To the Editors:

Tuberculosis (TB) has been declared a global emergency, increasing approximately 1% each year. There are evidences that TB is being underdiagnosed worldwide.[1,2] One of the reasons is the failure of health care workers to consider TB in the differential diagnosis of patients with respiratory symptoms.

Delay in the diagnosis of TB in HIV-infected people is an important contributor to the excess morbidity and mortality.[2,3]

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The main purpose of this prospective study was to define clinical and epidemiological characteristics that can guide physician to the rapid diagnosis of pulmonary TB in HIV patients.

During 18 months (from October 2004 to April 2006), all patients attending for unscheduled visits to an Infectious Diseases Division of a public Hospital in Argentina were asked if they present cough among their symptoms and if so, they were invited to participate in the study. Patients, who signed informed consent, filled a questionnaire and their clinical records were evaluated prospectively. Chest X-rays were classified according to the classification described by Tattevin, et al.[4] Epidemiological and clinical data were compared between HIV patients with TB coinfection and those with HIV and other diagnosis. X2 and *t* test were used to compare data.

During the period studied, 9245 unscheduled visits were recorded, with 286 patients presenting cough. Among the patients with cough, 40 did not sign the consent. Of the remaining who agreed to participate, 35 (13%) presented a TB diagnosis (positive sputum smear and/or positive sputum or blood culture for *M. tuberculosis*), 211 have a non-TB diagnosis (most of them with pneumocystis jiroveci pneumonia (PCP): n = 51, 24%, community acquired pneumonia: n = 70, 33%). Twenty-three of the TB patients were HIV coinfected.

When TB-HIV-coinfected patients were evaluated (Table 1) and compared with HIV-infected patients who have cough but non-TB diagnosis, statistical association with TB was found with hepatomegaly ($P = 0.005$); splenomegaly ($P = 0.003$); night sweats ($P = 0.001$); weight loss of more than 5 kg ($P = 0.003$; duration of symptoms between 15 and 30 days ($P = 0.03$) but not with longer time; elevate alkaline phosphatase ($P = 0.03$); chest X-ray pattern of typical ($P = 0.0003$) or compatible ($P = 0.013$) with TB; and previous contact with a patient with TB. We could not find association ($P > 0.05$) with hemoptysis, pulmonary physical examination, previous TB or incarceration, lower educational level, T lymphocytes (LT) CD4 count, HIV-1 viral load, number of previous opportunistic infections, or white cell count.

TABLE 1. Clinical and Biochemical Characteristics of HIV-Infected Patients With TB and Non-TB Diagnosis

Characteristic	TB Patients	Non-TB Patients	*P*
$CD4^+$ T lymphocytes (cell/mL)	153 (5–616)	202.5 (1–946)	0.415
HIV-1 VL (copies/mL)	14199.5	44280	0.988
Hepatomegaly	22%	4%	0.005
Splenomegaly	13%	0.5%	0.003
Night sweats	74%	38%	0.001
Weight loss >5kg	69%	43%	0.003
Symptoms 15–30 days	21%	9%	0.03
↑alkaline phosphatase	21%	2%	0.03
X-ray typical TB*	30%	4%	0.000
X-ray compatible TB†	39%	16%	0.013
Contact TB patient	21%	7%	0.02

*Typical of TB: (nodular, alveolar or interstitial infiltrates predominantly affecting the zones above the clavicle or upper zones; presence of cavitation affecting upper zones or the apical segment of the lower lobe).
†Compatible with TB: (enlarged hiliar nodes, pneumonic lesion, atelectasis, mass lesion, milliary, pleural exudates).

In countries with high TB incidence such as Argentina, TB diagnosis in HIV patients with pulmonary symptoms must be always thought but specially in those patients who refer having weight loss of more than 5 kg, night sweats, and symptoms duration between 15 and 30 days. This study also highlights the importance of the physical examination (looking for visceromegalies) and X-ray to guide physician to the diagnosis of TB.

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Patient-Selected Treatment Partners Did Not Protect Against Drug Resistance During First-Line NNRTI-Based HAART in a Randomized Trial

To the Editors:

We recently reported in a large randomized study that treatment partners had no durable effect on viral suppression despite improved adherence to antiretroviral (ARV) drug pick-up from the pharmacy.[1] In this report, we present the findings of a substudy designed to determine the impact of the treatment partners on ARV resistance. This substudy is important because resistance is an emerging problem in resource-limited settings,[2–5] and it is influenced by the pattern of nonadherence,[6,7] hence there is a need to identify adherence interventions that are associated with a reduced risk of ARV resistance.

The study setting, population, and procedures have been described in detail previously,[1] Briefly, treatment-naive HIV-1–infected patients initiating efavirenz-based or nevirapine-based highly active antiretroviral therapy (HAART) at the Jos University Teaching Hospital, Jos, Nigeria, were randomized to receive standard of care (SOC) or HAART assisted by patient-selected treatment partners (TPA). The treatment partners were asked to observe ingestion of ARV drugs at least once daily and assist with monthly drug pick-up from the pharmacy. For the current substudy, genotyping was conducted in patients experiencing virologic failure, defined as viral load >1000 copies per milliliter at week 24 of treatment. Viral RNA isolated from plasma with the COBAS AmpliPrep Total Nucleic Acid Isolation Kit (Roche Diagnostics, Basel, Switzerland) was used for sequence analysis of the genes encoding reverse transcriptase (RT, codons 1–240) and protease (PR, codons 1–99). HIV-1 RNA was amplified by a one-step reverse transcription–polymerase chain reaction using the TITAN One Tube Reverse Transcription polymerase chain reaction kit (Roche Diagnostics) and amplified fragments were sequenced using the BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems, Foster City, CA) on an ABI 3100 Genetic Analyzer (Applied Biosystems). The primers used are those recommended by the Agence Nationale de Recherche sur le SIDA and are available at www.hivfrenchresistance.org. Genetic subtypes were determined by phylogenetic tree analysis. The new PR and RT sequences were aligned with sequences from reference strains representing all subtypes and circulating recombinant forms with the CLUSTAL W program. PR and RT amino acid sequences were compared with a subtype B consensus reference (HXB2) and analyzed for resistance mutations described in the 2008 version of the International AIDS Society–United States of America list of mutations.[8] Major nucleos(t)ide reverse transcriptase (NRTI) and nonnucleoside reverse transcriptase (NNRTI) mutations as defined in the 2008 International AIDS Society–United States of America list of drug resistance mutations were included in the analysis. An association between the number of major NRTI or NNRTI mutations and intervention group was tested for using Mantel–Haenszel methods. The prevalence of wild-type and specific major

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TABLE 1. Drug Resistance Mutations During Virologic Failure at Week 24

	Treatment Partner (SOC) (n = 40)	Patient Administered Treatment (TPA) (n = 55)	Unadjusted *P* Value
Major NRTI mutations			
M184V/I	16 (40.0)	21 (38.2)	0.8576*
T69D	0	0	—
L74V	0	1 (1.8)	> 0.9999
K65R	1 (2.5)	2 (3.6)	> 0.9999
Q151M	0	0	—
M41L	1 (2.5)	1 (1.8)	> 0.9999
T215Y/F	2 (5.0)	3 (5.5)	> 0.9999
L210W	0	0	—
D67N	0	1 (1.8)	> 0.9999
K70R	1 (2.5)	1 (1.8)	> 0.9999
K219E/Q	0	1 (1.8)	> 0.9999
Major NNRTI mutations			
L100I	0	1 (1.8)	> 0.9999
K101E/H/P	3 (7.5)	5 (9.1)	> 0.9999
K103N	10 (25.0)	8 (14.6)	0.1992*
V106A/M	2 (5.0)	0	0.1747
V108I	1 (2.5)	3 (5.5)	0.6362
†Y181C/I/V	6 (15.0)	19 (34.6)	0.0327*‡
Y188C/L/H	1 (2.5)	0	0.4211
G190S/A	4 (10.0)	7 (12.1)	0.7557

*The *P* values were obtained using χ^2 tests. For the remaining *P* values found in the table, low expected cell counts warranted the use of Fisher exact tests.

†All the mutations were Y181C except 1 case of Y181I in a TPA subject.

‡Adjustment for multiple comparisons of this *P* value using Sidak correction = 0.4125.

mutations in each intervention group were compared using a series of Fisher exact tests. Adequate expected cell frequencies allowed for the use of χ^2 tests in some instances.

A total of 48 of 248 TPA subjects and 73 of 251 SOC subjects experienced virologic failure at week 24. HIV-1 subtypes were distributed similarly in the 2 groups: CRF02_AG (35% versus 44%), G (21% versus 21%), and CRF14_BG (15% versus 7%) for TPA and SOC, respectively; A1, CFR06_CPX, CRF09_CPX, and CRF_AE were present in 1%–6% of patients. The median viral load (copies/mL) at the time of virologic failure was 5110 for TPA and 4425 for SOC. The median CD4 cell counts (cell/mm^3) were 223 and 229 for TPA and SOC, respectively. Use of efavirenz versus nevirapine and zidovudine/lamivudine versus tenofovir/emtricitabine was similar in both groups ($P = 0.69$ and 0.93, respectively). Of the subjects who met the definition of virologic failure, 2 were excluded from the analysis because of incomplete data. Sequences from 24 subjects (7 TPA and 17 SOC) were not amplifiable. Results from 95 subjects (40 TPA and 55 SOC) were available for analysis, and the distribution of major NRTI and NNRTI mutations are shown in Table 1. Wild type was present in 35% of subjects in both TPA and SOC groups ($P = 0.96$). M184V/I mutation was present in 40% of TPA and 38% of SOC ($P = 0.86$). Other major NRTI mutations (41L, K65R, D67N, T69D, K70R, L74V, Q151M, T215 Y/F, L210W, and K219E/Q) were detected in 0%–5% of TPA and SOC ($P > 0.99$). Y181C/I/V was present in 15% vs. 35% of TPA and SOC, respectively (unadjusted $P = 0.03$). Given the 16 NNRTI resistance mutations examined, an adjustment for multiple comparisons using Sidak correction was made yielding a *P* value of 0.41 when testing for the equivalent prevalence of Y181C/I/V in TPA vs. SOC. K103N was detected in 25% vs. 15% ($P = 0.20$) and 190S/A in 10% vs. 13% ($P = 0.76$). The other major NNRTI mutations (L100I, K101E/H/P, V106A/M, V108I, Y188C/L/H) were present in 0%–9% in each group ($P > 0.15$). There was no association between having a treatment partner and the number of major NRTI mutations 0 = 53% vs. 56%; 1 = 43% vs. 33%; 2 = 5% vs. 9%; 3 = 0% vs. 2% for TPA and SOC, respectively ($P = 0.94$) or number of major NNRTI mutations 0 = 58% vs. 56%; 1 = 23% vs. 20%; 2 = 15% vs. 16%; 3 = 5% vs. 4%; 4 = 0% vs. 4% for TPA and SOC, respectively ($P = 0.79$).

This is the first study to our knowledge where the impact of TPA on ARV resistance in a resource-limited setting was evaluated. Major resistance mutations were common during virologic failure at week 24 in both study arms, and treatment partners were not protective. The unadjusted *P* value comparing the frequency of the Y181C mutation between treatment groups trended toward a lower prevalence in those with treatment partners, but this was inconclusive, and when coupled with the results of other inferential tests performed leaves scant evidence of a statistically significant association. Lack of an association between having treatment partners and emergence of resistance is consistent with our previous finding that treatment partners do not confer a durable benefit on viral suppression though there was better drug pick-up from the pharmacy.[1] The discordance between impact of treatment partners on adherence to drug pick-up versus virologic and resistance outcomes probably reflects the limited precision of drug pick-up as a surrogate for actual drug ingestion. The findings of this study should not be taken as proof that TPA have no role in the treatment of HIV-infected patients in resource-limited settings. Little is known about the potential impact of treatment partners on disclosure of HIV status, acceptance of HIV testing, destigmatization, and other behavioral variables that influence the dynamics of the HIV epidemic. Our findings may not apply to protease inhibitor–based regimens because the consequences of nonadherence may differ for protease inhibitor–based compared with NNRTI-based regimens.[6] In conclusion, treatment partners alone are unlikely to mitigate emergence of drug resistance during first-line NNRTI-based HAART in resource-limited settings or enhance preservation of second-line treatment options.

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Medical Costs Averted by HIV Prevention Efforts in the United States, 1991–2006

To the Editors:

The HIV epidemic has taken a terrible toll of human life lost and has imposed a substantial economic burden in the United States as measured by the lifetime medical costs of treating persons with HIV.[1–4] These lifetime cost estimates are based on data on health care utilization by individuals in different stages of HIV disease, from sources including the AIDS Cost and Services Utilization Survey,[1] the HIV Cost and Services Utilization Survey,[5] and the HIV Research Network.[6] The costs associated with health care utilization in each disease stage are summed across all disease stages from infection to death to calculate the costs expected to be incurred by a person infected with HIV. Disease progression models are used to predict the length of each disease stage and the efficacy of HIV treatment in slowing disease progression.

A rough measure of the effect of HIV prevention programs in the United States can be estimated by comparing the difference between the number of infections that have occurred with the number that might have occurred in the absence of these programs based on changes in HIV transmission rates.[7–9] Plausible estimates of the number of infections averted can be derived and combined with estimates of life-time treatment costs to calculate the overall treatment cost savings from HIV infections averted. We present these calculations for the period 1991–2006.

Table 1 gives estimates of HIV incidence, prevalence, transmission rates, and infections averted from 1991–2006.[7–11] I (x) is the number of new infections in year x, prevalence, P (x), is the number of persons living with HIV in year x, and the transmission rate for year x, T (x), is calculated as $[I(x)/P(x)] \times 100$. We used updated incidence estimates from the Centers for Disease Control and Prevention calculated in multiyear time blocks that were chosen based on prior information about the likely shape of the incidence curve and the evaluation of models with different assumptions. Although this approach may have caused some discontinuities in the incidence data, the results are similar to other estimates.[10] Prevalence was estimated as the number of existing cases of HIV plus the number of new cases [I (x)] minus the number of deaths among persons with HIV. Deaths for persons with AIDS were derived from Centers for Disease Control and Prevention's HIV surveillance database, whereas deaths for persons with HIV (not AIDS) were calculated by multiplying the number of persons living with HIV (not AIDS) in a given year by a general population mortality rate of 427.1 per 100,000 persons 45–54 years old.[9]

Infections averted by US prevention programs were calculated in the base case under the assumption that the US HIV annual transmission rate would not have dropped below 8.2, the 2007 global transmission rate across all nations,[12–13] in the absence of these programs. This global transmission rate is based on Joint United Nations Program on HIV/AIDS/World Health Organization estimates of global HIV incidence and prevalence that draw on all pertinent available data and incorporate substantial revisions in estimation methodology resulting in more accurate and refined estimates.[14,15] These estimates, which are derived from countries with both generalized and concentrated epidemics, apply to a period in which there has been substantial investment in HIV prevention and treatment by the Global Fund and PEPFAR. Thus, we are using a comparison transmission rate that is relatively conservative. The difference between actual and projected HIV incidence in the United States occurred from 1991 to 2006 and resulted in an estimate of approximately 362,000 infections averted (Table 1), which is within the range of previously published estimates.[7]

Life-time HIV treatment cost estimates developed at different points during the epidemic have incorporated varying assumptions about awareness of infection, life expectancy, and treatment regimens for persons with HIV. Guinan et al[2] used the cost estimates by Hellinger[1] that reflected the pre-antiretroviral therapy (ART) treatment regimens in the early 1990s. Hellinger[1] calculated HIV treatment costs by disease stage with an assumed life expectancy of 12.4 years from the time of infection. Guinan et al[2] adjusted these costs by assuming that patients with CD4 counts greater than 500 were unaware of their disease for 6 years, aware but asymptomatic for the next 3 years (CD4 count between 200 and 500), symptomatic for 1 more year before AIDS (CD4 count less than 200), and had AIDS for 2 years. Using a 5% discount rate to calculate the present value of these

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TABLE 1. HIV Infections Prevented and Their Medical Costs, 1991–2006 (2009 Dollars)

Base Case Analysis, Global Transmission Rate								
Year	HIV Incidence I (x)	HIV Prevalence P (x)	HIV Transmission Rate T (x)	Projected Transmission Rate T (x)	Projected Incidence I (x)	Cases of HIV Infection Averted	Base Case Life-Time Costs	Base Case Cost of HIV Infections Averted (billion $)
1991	48,700	733,010	6.6	8.2	59,074	10,374	$321,276	$3.3
1992	48,700	739,655	6.6	8.2	60,620	11,920	$321,276	$3.8
1993	48,700	742,510	6.6	8.2	61,851	13,151	$321,276	$4.2
1994	48,800	740,600	6.6	8.2	62,780	13,980	$321,276	$4.5
1995	48,800	737,624	6.6	8.2	63,266	14,466	$321,276	$4.6
1996	48,800	747,525	6.5	8.2	63,639	14,839	$367,134	$5.4
1997	58,400	782,207	7.5	8.2	65,263	6,863	$367,134	$2.5
1998	58,400	820,080	7.1	8.2	68,462	10,062	$367,134	$3.7
1999	58,400	858,494	6.8	8.2	72,209	13,809	$367,134	$5.1
2000	55,300	894,247	6.2	8.2	76,299	20,999	$367,134	$7.7
2001	55,300	929,739	6.0	8.2	80,737	25,437	$367,134	$9.3
2002	55,300	965,612	5.7	8.2	85,482	30,182	$367,134	$11.1
2003	55,400	1,001,784	5.5	8.2	90,616	35,216	$367,134	$12.9
2004	55,400	1,038,192	5.3	8.2	96,148	40,748	$367,134	$15.0
2005	55,400	1,074,647	5.2	8.2	102,112	46,712	$367,134	$17.1
2006	55,400	1,113,297	5.0	8.2	108,519	53,119	$367,134	$19.5
Total	855,200				1,217,078	361,878		$129.9

Sensitivity Analysis, 1990 Transmission Rate					Sensitivity Analysis, 1997 Transmission Rate				
Projected Transmission Rate T (x), 1990 TR	Projected Incidence I (x), 1990 TR	Cases of HIV Infection Averted, 1990 TR	Base Case Lifetime Costs	Cost of HIV Infections Averted, 1990 TR (billion $)	Projected Transmission Rate T (x), 1997 TR	Projected Incidence I (x), 1997 TR	Cases of HIV Infection Averted, 1997 TR	Base Case Lifetime Costs	Cost of HIV Infections Averted, 1997 TR (billion $)
11.7	84,200	35,500	$321,276	$11.4	7.5	53,906	5,206	$321,276	$1.7
11.7	89,184	40,484	$321,276	$13.0	7.5	54,951	6,251	$321,276	$2.0
11.7	93,922	45,222	$321,276	$14.5	7.5	55,696	6,996	$321,276	$2.2
11.7	98,400	49,600	$321,276	$15.9	7.5	56,159	7,359	$321,276	$2.4
11.7	102,351	53,551	$321,276	$17.2	7.5	56,219	7,419	$321,276	$2.4
11.7	106,265	57,465	$367,134	$21.1	7.5	56,176	7,376	$367,134	$2.7
11.7	112,483	54,083	$367,134	$19.9	7.5	57,228	−1,172	$367,134	−$0.4
11.7	121,793	63,393	$367,134	$23.3	7.5	59,636	1,236	$367,134	$0.5
11.7	132,592	74,192	$367,134	$27.2	7.5	62,484	4,084	$367,134	$1.5
11.7	144,608	89,308	$367,134	$32.8	7.5	65,586	10,286	$367,134	$3.8
11.7	157,942	102,642	$367,134	$37.7	7.5	68,942	13,642	$367,134	$5.0
11.7	172,604	117,304	$367,134	$43.1	7.5	72,511	17,211	$367,134	$6.3
11.7	188,855	133,455	$367,134	$49.0	7.5	76,357	20,957	$367,134	$7.7
11.7	206,831	151,431	$367,134	$55.6	7.5	80,483	25,083	$367,134	$9.2
11.7	226,727	171,327	$367,134	$62.9	7.5	84,909	29,509	$367,134	$10.8
11.7	248,704	193,304	$367,134	$71.0	7.5	89,640	34,240	$367,134	$12.6
	2,287,461	1,432,261		$515.5		1,050,883	195,683		$70.3

TR, transmission rate.

costs, their estimate of these treatment costs was $55,640 (1992 dollars).

Holtgrave and Pinkerton[3] developed a range of treatment cost estimates that reflected initial treatment with ART regimens in the mid-1990s. Their intermediate cost scenario represented current treatment in 1996–1997 and was used as their base case. They defined disease stage by awareness of infection, CD4 count, and type of drug therapy and assumed a life expectancy of 16 years from the time of infection. Using a 3% discount rate, their present-value treatment cost estimate was $195,188 (1996 dollars).

Schackman et al[4] used HIV Research Network utilization data, cost data from different sources, and the Cost-Effectiveness of Preventing AIDS Complications disease progression model to estimate HIV treatment costs in the era of established ART regimens. Using a 3% discount rate and a life expectancy of 32.1 years from the time of infection, they estimated the present value of HIV treatment costs to be $303,100 (2004 dollars).

Because these estimates were developed with similar methodologies, they were applied to the number of infections averted from 1991 to 2006. The Guinan et al[2] costs were first re-estimated with a 3% discount rate for consistency with the other 2 estimates. All estimates were updated to 2009 dollars using the medical care component of the Consumer Price Index.[16]

The base case estimate of $129.9 billion for overall medical costs saved was derived by applying the Holtgrave and Pinkerton[3] estimate of $321,276 (2009 dollars) to the years 1991–1995, whereas the Schackman et al[4] estimate of $367,134 (2009 dollars) was applied to the years 1996–2006 (Table 1). Because Guinan et al[2] assumed that HIV-infected persons would be unaware of their status for 6 years, we assumed individuals infected in 1991–1995 would begin treatment in the

late 1990s with the ART regimens reflected in the Holtgrave and Pinkerton[3] cost estimates. Given the Schackman et al[4] assumption of 8.1 years from time of infection to diagnosis, persons infected from 1996 to 2006 would begin treatment with the regimens included in the Schackman et al[4] costs. The overall estimate of $129.9 billion is conservative because some HIV patients in the earlier period would have adopted the more expensive treatment regimens as they were developed over the course of their lives. A lower-bound estimate for overall medical costs saved of approximately $49 billion was derived by applying the updated Guinan et al[2] estimate of $134,928 (2009 dollars) to all 16 years of infections prevented, whereas an upper-bound estimate of approximately $133 billion was derived by applying the Schackman et al[4] estimate of $367,134 (2009 dollars) to the data. This range of estimates shows the cost differences associated with treatments that evolved from single drug therapy in the early 1990s to the multidrug regimens used a decade later.

We also conducted sensitivity analyses in which we assumed that the annual transmission rate would not have dropped below the US 1990 rate of 11.7 or below the US 1997 rate of 7.5. In the former case, there would have been approximately 1.4 million infections and $516 billion (2009 dollars) of costs averted, whereas in the latter case, 196,000 infections and $70 billion (2009 dollars) in costs would have been averted. The impact of the changes in transmission rates over the course of the epidemic on the costs averted is substantial.

The $129.9 billion base case estimate reflects only medical costs averted, not net savings, because we did not subtract the cost of HIV prevention programs. We also did not include any costs of lost productivity in the estimates. One estimate of these costs is $353.2 billion (2009 dollars) based on the cost-per-case mortality-related productivity loss estimates of Hutchinson et al.[17] The decline in transmission rates and the estimated infections averted in the analysis could have been influenced by clinical therapies that reduced the viral load of infected persons, although the rise in the HIV transmission rate in 1997 indicates one should be cautious about accepting this hypothesis at the national level. Our base case estimate of medical costs alone shows the substantial impact these cases of HIV would have had on the US economy had they not been averted.

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