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1. Orriols L, Salmi LR, Philip P, et al. The impact of medicinal drugs on traffic safety: a systematic review of epidemiological studies. *Pharmacoepidemiol Drug Saf.* 2009;18(8):647-658.
2. Gustavsen I, Bramness JG, Skurtveit S, Engeland A, Neutel I, Mørland J. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. *Sleep Med.* 2008;9(8):818-822.
3. Orriols L, Philip P, Moore N, et al; CESIR Research Group. Benzodiazepine-

like hypnotics and the associated risk of road traffic accidents. *Clin Pharmacol Ther.* 2011;89(4):595-601.

4. Barbone F, McMahon AD, Davey PG, et al. Association of road-traffic accidents with benzodiazepine use. *Lancet.* 1998;352(9137):1331-1336.
5. Bonnett LJ, Tudur-Smith C, Williamson PR, Marson AG. Risk of recurrence after a first seizure and implications for driving: further analysis of the Multicentre study of early Epilepsy and Single Seizures. *BMJ.* 2010;341:c6477.
6. Arrêté du 8 août 2008 pris pour l'application de l'article R. 5121-139 du code de la santé publique et relatif à l'apposition d'un pictogramme sur le conditionnement extérieur de certains médicaments et produits. *Journal Officiel de la République Française.* 2008. www.journal-officiel.gov.fr. Accessed May 3, 2012.
7. Orriols L, Delorme B, Gadegbeku B, et al; CESIR Research Group. Prescription medicines and the risk of road traffic crashes: a French registry-based study. *PLoS Med.* 2010;7(11):e1000366.
8. Moore N, Pierfite C, Pehourcq F, Lagnaoui R, Bégaud B. Comparison of patient questionnaires, medical records, and plasma assays in assessing exposure to benzodiazepines in elderly subjects. *Clin Pharmacol Ther.* 2001;69(6):445-450.
9. Moore N, Masson H, Noblet C, Joannidis R. What medicines do patients really take? a comparison of free form vs oriented questionnaires. *Pos Marketing Surveillance.* 1993;7:355-362.

Safety Against Cervical Precancer and Cancer Following Negative Human Papillomavirus and Papanicolaou Test Results in Human Immunodeficiency Virus-Infected Women

The American Cancer Society (ACS) first recommended cotesting (cervical cytologic and human papillomavirus [HPV] DNA testing) as an acceptable alternative to routine cervical cytologic testing alone for cervical cancer screening in 2002.¹ The ACS recommendations included extending the screening interval to not less than 3 years for those women who tested negative for both tests ("negative cotest").

Human immunodeficiency virus (HIV) infection, and its clinical manifestation of AIDS, is a known risk factor for cervical precancer² and cancer,³ and cervical cancer is considered an AIDS-defining malignancy. Current guidelines⁴ for cervical cancer screening recommend Papanicolaou (Pap) testing twice during the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter. It is unknown whether a negative cotest result might provide similar safety for HIV-infected women as it does for HIV-negative women. Thus, the objective of this analysis was to assess the risk of cervical precancer and cancer following a negative cotest result in HIV-seropositive women 30 years and older.

Methods. In January 2003, Kaiser Permanente Northern California (KPNC) introduced cotesting using Hybrid Capture 2 (Qiagen) and conventional Pap testing, with a screening interval extension to 3 years after a negative cotest result. Papanicolaou test results were interpreted according to the 2001 Bethesda System.⁵ Annual Pap tests continued to be available as an option. By early 2007, 95% of KPNC screening participants 30 years and older elected cotesting at 3-year intervals in preference to annual Pap testing. For women who tested positive for HPV and had negative Pap test results (HPV+/Pap-), management evolved from annual follow-up with retesting, to recommending colposcopy after 2 HPV+/Pap- screening results in 2006, to mandatory colposcopy after 2 HPV+/Pap- screening results in 2008, according to interim guidance.⁶

Table. Results for HPV and Papanicolaou Cotesting for 245 HIV-Infected Women 30 Years and Older Who Had a Preceding Negative Cotest Result (Concurrent HPV- and Pap- Test Results)^a

Second Cotest Result	No. (%)	Third Cotest Result	No. (%)
HPV-/Pap-	202 (82)		
HPV-/ASC-US ^b	9 (4)	HPV-/Pap-	5 (56)
		HPV-/ASC-US	1 (11)
		HPV-/LSIL+	1 (11)
		HPV+/Pap-	0
		HPV+/ASC-US+	1 (11)
		Missing	1 (11)
HPV-/LSIL+	0		
HPV+/Pap- ^b	16 (7)	HPV-/Pap-	6 (38)
		HPV-/ASC-US	0
		HPV-/LSIL+	0
		HPV+/Pap-	5 (31)
		HPV+/ASC-US+ ^c	3 (19)
		Missing	5 (31)
HPV+/Pap+	11 (4)		
HPV-/Pap unspecified	2 (1)		
HPV missing/Pap-	2 (1)		
HPV missing/ASC-US+	1 (0)		
HPV and Pap missing	2 (1)		

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; ASC-US+, ASC-US or more severe cytology; HIV, human immunodeficiency virus; HPV-, human papillomavirus negative; HPV+, human papillomavirus positive; LSIL+, low-grade squamous intraepithelial lesion or more severe cytology; Pap-, Papanicolaou test result negative; Pap+, Papanicolaou test result positive.

^aThirty-one percent of women were aged 30 to 39 years; 44%, aged 40 to 49 years; 20%, aged 50 to 59 years; and 5%, 60 years and older.

^bWomen with these results undergo a 1-year follow-up rather than immediate colposcopy.

^cIncludes 1 case of high-grade squamous intraepithelial lesion cytology (histologic diagnosis was CIN1).

There were no special recommendations for cervical cancer screening of HIV-infected women at KPNC, so those 30 years and older underwent routine cotesting. We used electronic medical records to identify HIV-infected women who had a negative cotest result to examine the safety it conveys.

We calculated the risk of histologically confirmed cervical (CIN2) or more severe (CIN2+) intraepithelial neoplasia and high-grade squamous intraepithelial lesion (HSIL) cytology and/or CIN2+ histology (HSIL+) with binomial exact 95% confidence intervals.

The KPNC Institutional Review Board and Western Institutional Review Board (for Dr Castle) approved the use of these data. The KPNC HIV Steering Committee also approved the use of these data.

Results. We identified 245 women 30 years and older who had negative HPV and Pap test ("negative cotest") results and underwent a second cotest between 2003 and 2010. The second cotest was done at 24.4 months (mean), 23 months (median), 15 to 35 months (interquartile range [IQR]), and 5 to 42 months (range) after the first cotest; 32% of women had a cotest 30 months or later. CD4 cell counts were 519.7/ μ L (mean), 475/ μ L (median), 338/ μ L to 681/ μ L (IQR), and 4/ μ L to 1380/ μ L (range); the dis-

tribution of CD4 cell counts was 9% with lower than 200/ μ L, 44% with 200/ μ L to 499/ μ L, and 47% with 500/ μ L or higher. The CD4 cell measurements were conducted a mean of 3.1 months after and a median of 0.2 months before the first cotest. Of the 92 women whose HIV viral load data we were able to retrieve, measurements were 20 274.5/mL (mean), 7552.5/mL (median), 766/mL to 32 363.5/mL (IQR), and 75/mL to 352 531/mL (range). The HIV viral load measurement was conducted a mean 8.2 and a median of 0.2 months after the first cotest.

We found Pap test results for 241 women (21 [8.7%] with a positive result) and HPV results for 240 women (27 [11.3%] with a positive result). The combined HPV and Pap test results for the second cotest and the third cotest results for those women who underwent a 12-month follow-up per current guidelines (HPV+/Pap- and HPV-/atypical squamous cells of undetermined significance) are given in the **Table**. For 236 women with a complete follow-up, we found no cases of histologically confirmed CIN2+, for a CIN2+ risk of 0.0% (95% CI, 0.0%-1.6%), and 1 case of HSIL cytology (on the third cotest as a follow-up of HPV+/Pap- result on the second cotest), for a risk of HSIL cytology of 0.4% (95% CI, 0.0%-2.3%). Among the 78 women with a complete follow-up of 30 months or more after the first cotest, there was 0% (95% CI, 0.0%-4.6%) risk for CIN2+.

Comment. In this population of HIV-infected women 30 years and older, we found that a negative cotest result conferred excellent safety against cervical precancer and cancer, which is akin to the safety cotesting provides HIV-negative populations.⁷ These findings are consistent with our understanding of the natural history of HPV and cervical cancer,⁸ in which CIN2+ only develops several years after a newly detected HPV infection. While more data are needed, these results suggest that it may be acceptable and safe to extend cervical cancer screening intervals by including HPV testing, thereby minimizing the harms of screening.

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1. Saslow D, Runowicz CD, Solomon D, et al; American Cancer Society. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin.* 2002;52(6):342-362.
2. Hawes SE, Critchlow CW, Faye Niang MA, et al. Increased risk of high-grade cervical squamous intraepithelial lesions and invasive cervical cancer among African women with human immunodeficiency virus type 1 and 2 infections. *J Infect Dis.* 2003;188(4):555-563.
3. Shiels MS, Pfeiffer RM, Hall HI, et al. Proportions of Kaposi sarcoma, selected non-Hodgkin lymphomas, and cervical cancer in the United States occurring in persons with AIDS, 1980-2007. *JAMA.* 2011;305(14):1450-1459.
4. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207.
5. Solomon D, Davey D, Kurman R, et al; Forum Group Members; Bethesda 2001 Workshop. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA.* 2002;287(16):2114-2119.
6. Wright TC Jr, Schiffman M, Solomon D, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. *Obstet Gynecol.* 2004;103(2):304-309.
7. Katki HA, Kinney WK, Fetterman B, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol.* 2011;12(7):663-672.
8. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet.* 2007;370(9590):890-907.

COMMENTS AND OPINIONS

Percutaneous Coronary Intervention for Stable Coronary Artery Disease: The Debate Continues

We read the recent meta-analysis by Drs Stergiopoulos and Brown¹ comparing initial medical therapy with initial stent implantation for stable coronary artery disease (CAD) as well as the accompanying Invited Commentary by Dr Boden² with great interest. However, we are concerned that the choice of trials does not support the conclusions arrived at. We agree with Dr Boden that any meta-analysis comparing optimal medical therapy (OMT) alone with OMT and per-

cutaneous coronary intervention (PCI) in patients with stable CAD that fails to exclude both acute and post-myocardial infarction (MI) trials suffers from a significant methodological flaw.

Application of this criteria to the current meta-analysis reveals that the trials included represent a heterogeneous population, particularly the Open Artery Trial (TOAT), Desobstruction Coronnaire en Post-Infarctus (DECOPI) trial, and Occluded Artery Trial (OAT), which together account for a third of the patients (2333 of a total 7229 patients) included in this meta-analysis. The largest of these, the OAT (N=2166), was clearly a trial of stable but high-risk patients, ie, depressed ejection fraction or proximal occlusion of a major epicardial vessel, following completed infarcts with total occlusion of the infarct-related vessel. Enrollment in this trial did not require demonstration of ischemia or symptoms. In fact, patients with clinically significant ischemia or angina at rest were excluded.³ Likewise, the DECOPI trial (N=212) was a trial of patients with recent completed infarcts with an occluded infarct-related artery and excluded patients with spontaneous or low-level ischemia.⁴ Similarly the TOAT Study (N=66 patients) included patients with an occluded left anterior descending artery following a recent MI and no evidence of ischemia on a modified Bruce treadmill exercise test.⁵ The OAT and DECOPI trial are the basis for the current practice of not intervening on an occluded artery 3 to 28 days after MI in stable patients. These patients with a recent infarct, an occluded vessel, and no clinically significant ischemia are very different from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) population with obstructive CAD and chronic stable angina or demonstrable ischemia.⁶ The co-mingling of these populations prevents us from drawing any meaningful conclusions.

The complexity of the spectrum of stable CAD and the failure of a one-size-fits-all approach is clear in the appropriateness criteria for revascularization in stable CAD put forth by the American College of Cardiology.

Hopefully the publication of the recently halted FAME II trial (Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment vs Optimal Medical Treatment Alone in Patients With Stable Coronary Artery Disease), using fractional flow reserve-guided lesion assessment and then randomization to PCI + OMT vs OMT alone, will enlighten and better inform our decision making in stable CAD.

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