

Perspective

Screening for Anal Dysplasia Associated with Human Papillomavirus

Anal dysplasia associated with human papillomavirus (HPV) infection occurs in substantial proportions of HIV-infected men and women and poses risk for anal carcinoma. Whether to routinely screen for HPV-associated anal dysplasia in this population, however, remains a debated question. Anal dysplasia is detectable by Pap screening and colposcopic biopsy; as Pap testing results have relatively low reproducibility, 2 baseline tests may be prudent. Screening should also ascertain risk factors for dysplasia, including HIV infection, degree of immunosuppres-

sion, and history of prior anal disease. Although treatment options for anal dysplasia are limited by morbidity and high recurrence rates, early detection may permit better tolerance of therapy, and current estimates indicate that routine screening for the condition would be cost-effective. In addition, emerging immunologic therapies offer hope of more effective future treatment. This article summarizes a presentation given by Wm. Christopher Mathews, MD, MSPH, at the November 2002 International AIDS Society–USA course in San Diego.

low-grade squamous intraepithelial lesions (LSIL) and condyloma, intermediate-risk types (31, 33, 35, 45, 51, 52, and 56), and the high-risk types (16 and 18) that are found in approximately two-thirds of cases of invasive cervical cancer.

The newly revised Bethesda System of cervical cytologic classification (Solomon et al, *JAMA*, 2002) also applies to anal intraepithelial neoplasia. In this system, atypical squamous cells (ASC) are classified as “of undetermined significance” (ASCUS) or as “cannot exclude HSIL” (ASC-H). Squamous intraepithelial lesions are graded as LSIL, HSIL, or squamous cell carcinoma. LSIL indicates mild dysplasia (HPV cellular changes) and is equivalent to the cervical intraepithelial neoplasia (CIN) 1 category in the World Health Organization (WHO) histopathologic classification system. HSIL is categorized as either moderate dysplasia, equivalent to CIN 2 in the WHO system, or severe dysplasia, equivalent to CIN 3. The distinction between severe dysplasia and carcinoma in situ, also CIN 3, is very narrow, and the same lesion might be judged as severe dysplasia by one pathologist and carcinoma in situ by another. Cytologically, ASCUS is characterized by features of both LSIL and HSIL with the features being diagnostic of neither. LSIL is characterized by relatively little basal cell proliferation and atypia; the effects of HPV are observed as “koilocytes,” featuring an irregular enlarged nucleus with a clear halo. Most LSILs spontaneously regress. HSIL is characterized by increasingly severe atypia, abnormal mitotic activity in the superficial layers, and immature basaloid cells.

Under the Bethesda System, it is recommended that patients with ASCUS findings on Pap testing undergo HPV testing. HPV-positive patients should undergo colposcopy or repeat Pap testing at 6 and 12 months, and HPV-negative patients should have

Evidence-based public health decisions regarding whether screening programs for a particular health condition should be recommended are influenced by a number of factors:

1. How important is the health condition to be sought in terms of frequency, morbidity, and mortality?
2. How good is the screening test in terms of accuracy, safety, simplicity, acceptability to patients and health care practitioners, labeling effects (ie, social and psychologic effects on the patient from positive test results), and cost?
3. How strong is the evidence that outcome of the condition is improved if treatment is given after screening versus at the time the patient presents with symptoms?

Human papillomavirus (HPV)-associated anal dysplasia is a common condition in HIV-infected patients and is associated with increased risk for anal carcinoma. Whether to routinely screen for

HPV-associated anal dysplasia remains a debated issue.

What Is the Incidence, Morbidity, and Mortality of HPV-Associated Anal Dysplasia?

Cervical cancer serves as a biologic and an epidemiologic model for anal carcinoma and its precursors. The current incidence of cervical cancer in the United States is approximately 8 cases per 100,000 people. The incidence of anal cancer in men who had sex with men (MSM) prior to the HIV epidemic was 35 per 100,000—an incidence rate similar to that of cervical cancer before routine Pap testing was implemented for the latter (Daling et al, *N Engl J Med*, 1987). The rate of anal cancer in HIV-infected MSM is approximately twice that in HIV-seronegative MSM (Goedert et al, *Lancet*, 1998).

Cervical and anal cancers have similar histologies, with both frequently arising in the squamocolumnar junction (transformation zone) and both being strongly associated with oncogenic strains of HPV. High-grade squamous intraepithelial lesions (HSIL) are a proven precursor to cervical cancer and are strongly suspected to be a precursor to anal cancer. HPV types include low-risk types (6 and 11) associated with

Dr Mathews is Professor of Clinical Medicine at the University of California San Diego Medical Center and Director of the UCSD Owen Clinic and of the UCSD AIDS Education and Training Center.

repeat Pap testing at 12 months. Patients with ASC-H should be immediately referred to colposcopy without HPV testing.

Data on the natural history of CIN, derived from 64 studies involving 15,473 CIN cases and 274 carcinoma cases followed for less than 1 year to 12 years, are shown in Table 1 (Östör, *Int J Gynecol Pathol*, 1993). Progression to carcinoma in situ or invasive disease is more frequent in the CIN 2 and CIN 3 categories. Comparable progression rates for anal intraepithelial neoplasia are unknown but likely to be similar.

HPV and Anal Dysplasia in HIV-Infected Patients

The cell-mediated immune response to HPV modulates the development of squamous intraepithelial lesions. A study in women with cervical HPV-16 showed that those with HPV-specific immune response were less likely to develop squamous intraepithelial lesions. HIV-induced expression of cytokines (eg, interleukin-6) may modulate HPV gene expression, and the HIV Tat protein may potentiate expression of HPV E6 and E7 gene products that are considered to be crucial in inducing chromosomal instability.

In a study reported in 1994 (Williams et al, *Obstet Gynecol*), 77% of 54 HIV-infected women had HPV infection detected by polymerase chain reaction (PCR) test. Of those with both cervical and anal HPV, the same HPV types were found in only 50%. In another study reported in 1996 (Melbye et al, *Int J Cancer*), 12.1% of 124 women had abnormal anal cytology. Risk factors for anal intraepithelial neoplasia were HIV seropositivity, low CD4+ cell count,

and HPV positivity by PCR. Data on HPV infection in MSM in the pre-potent antiretroviral therapy era indicate that 93% of HIV-infected men and 61% of HIV-seronegative men had anal HPV detected by PCR, with HPV-16 being the most common type. Infection with multiple HPV types was found in 73% of HIV-infected men, with the frequency increasing with lower CD4+ cell counts, and in 23% of HIV-seronegative men (Palefsky et al, *J Infect Dis*, 1998). Palefsky and colleagues (*J Acquir Immune Defic Syndr Hum Retroviral*, 1998) found that LSIL or HSIL was present in 124 of 346 (36%) HIV-infected MSM compared with 19 of 262 (7%) HIV-seronegative MSM. Compared with HIV-seronegative patients (relative risk 1.0), relative risk for LSIL or HSIL increased with decreasing CD4+ cell count in HIV-infected patients, to 3.9 at cell counts greater than 500/ μ L, 5.6 at 200 to 500/ μ L, and 7.3 at less than 200/ μ L.

Figure 1 shows the prevalence of LSIL or HSIL in approximately 650 HIV-infected patients screened at the University of California San Diego Owen Clinic according to sex, MSM status, and CD4+ cell count. These data show a high frequency of LSIL or HSIL among male patients not reporting sex with men as a risk factor, suggesting that screening of only MSM would result in missing anal dysplasia in a significant proportion of patients. The relationship between LSIL or HSIL and CD4+ cell count is consistent with other studies. In 49 biopsies performed at the Owen Clinic, carcinoma in situ was found in 0 of 2 patients with normal Pap findings, 0 of 2 with ASCUS, 4 of 20 (20%) with LSIL, and 4 of 25 (16%) with HSIL (16% overall; Mathews et al, 9th CROI, 2002).

The Owen Clinic's screening policy now is to refer any patient with ASCUS, LSIL, or HSIL for colposcopy.

Impact of Potent Antiretroviral Therapy on Anal Squamous Intraepithelial Lesions

Potent antiretroviral therapy leading to immune reconstitution including HPV-specific response might induce regression of anal squamous intraepithelial lesions and thus reduce rates of progression to anal cancer. On the other hand, if treatment-related immune reconstitution does not affect pathogenesis of HPV-associated dysplasia, prolonged survival in HIV-infected patients is likely to be accompanied by increased frequency of anal cancer. Anecdotal observations currently suggest that the frequency of invasive anal cancer has increased with greater patient longevity. One study reported by Palefsky and colleagues (*Semin Oncol*, 2000), however, indicates some potential for disease regression. Evaluation at 6 months after the start of potent antiretroviral therapy in 28 men with HSIL at the start of treatment showed no change in 57%, LSIL in 21%, ASCUS in 18%, and normal findings in 4%. Patients who showed regression had higher CD4+ cell counts at baseline than those who did not show regression.

Although these are the only available data on the effects of potent therapy in patients with anal squamous intraepithelial lesions, Minkoff and colleagues (*AIDS*, 2001) have reported findings on cervical squamous intraepithelial lesions in the Women's Interagency HIV Study of 741 HIV-infected women with at least 1 oncogenic HPV strain. These women were followed with biannual Pap smears, and findings in consecutive pairs of tests were analyzed according to potent therapy status. Patients were defined as "off therapy" if they were not receiving therapy or were seen prior to therapy and as "on therapy" during any visit after start of therapy. This study found that women with persistent HPV were more likely to have lesion progression. After adjustment for CD4+ cell count and Pap status, patients on potent therapy were 40% more likely to have lesion regression and had an odds ratio of 0.68 for lesion progression compared with those off therapy.

Table 1. Natural History of Cervical Intraepithelial Neoplasia (CIN), by World Health Organization Histopathologic Classification

Classification	Regression	Persistence	Progression to Carcinoma in Situ	Progression to Invasive Disease
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3	32%	<56%	–	>12%

Adapted from Östör, *Int J Gynecol Pathol*, 1993.

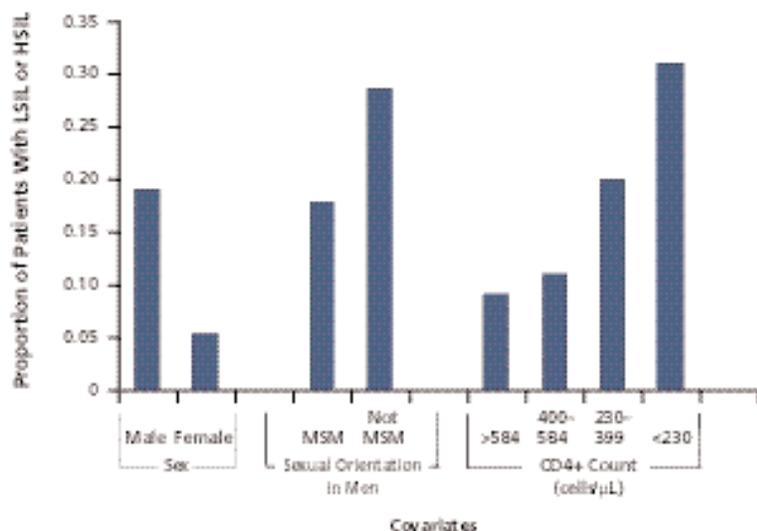


Figure 1. Prevalence of low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL) among approximately 650 HIV-infected patients by sex, classification as men who have sex with men (MSM) versus not MSM for men only, and CD4+ cell count. $P=.036$ for sex; $P=.088$ for MSM; $P<.0001$ for CD4+ cell count. Adapted with permission from Mathews et al, 9th CROI, 2002.

What Are the Efficacy and Effects of Anal Dysplasia Screening Tests?

The decision regarding who to screen for anal dysplasia depends on the probability of finding the disease in particular populations. There is a clear rationale for screening both HIV-infected and HIV-seronegative MSM. There is also a clear rationale for screening HIV-infected women with a history of anal receptive intercourse, anogenital warts or HPV infection, or cervical dysplasia. However, a case can also be made for screening all HIV-infected men and women, particularly given the unreliable nature of histories of sexual behavior. (Chin-Hong and Palefsky, *Clin Infect Dis*, 2002).

Components of screening evaluations include Pap tests (performed via conventional methods or using the liquid medium technique), digital rectal examinations, and high-resolution anoscopy. HPV testing has an uncertain role in screening. With regard to reproducibility of Pap testing, the sensitivity of cervical cytology to detect CIN 2 or 3 is estimated at a reliability coefficient of 0.67 to 0.76. Dr Mathews and colleagues have found that the reproducibility of anal Pap testing is lower,

with a kappa statistic agreement of 0.30 between single repeat tests for HSIL/LSIL versus ASCUS/normal cytology found in testing of 42 patients (9th CROI, 2002). The Owen Clinic has thus instituted a practice of obtaining 2 baseline anal Pap tests in all patients screened.

Screening for anal squamous intraepithelial lesions begins with ascertaining risk factors, including HIV status and degree of immune suppression; history of anogenital warts, anal receptive intercourse, and prior cervical or anal squamous intraepithelial lesions; symptoms such as discharge, pain, or bleeding; and history of tobacco use. Risk factors for other anal sexually transmitted diseases should also be ascertained. Dysplasia screening presents an opportunity to screen for other anal sexually transmitted diseases, and Dr Mathews and colleagues are currently studying the diagnostic yield and cost-effectiveness of such joint screening. Use of the liquid medium technique for Pap testing allows use of the same sample for PCR testing for gonorrhea and chlamydia infections. Since dysplasia is not confined to the anal canal, physical evaluation should include examination of the perianal area, perineum, and genitalia, including the inguinal nodes. The Pap smear should not be taken after douch-

ing, enema, or anal intercourse, since any of these might remove the superficial abnormal cells being sought. The sample should be taken using a Dacron, rather than cotton, swab moistened with ordinary tap water. The swab should be inserted at least 1.5 to 2 inches into the anal canal (best results might be achieved by insertion to the posterior wall of the rectum) and withdrawn slowly while rotated in a spiral fashion. The swab should be rolled quickly across a slide, which should then be dipped in fixative.

High-resolution anoscopy should be performed after digital rectal examination using a lidocaine and water-based lubricant mixture. After insertion of the anoscope, a 4x4-cm gauze pad that has been soaked in ordinary 3% vinegar solution and wrapped around a cotton swab is inserted through the scope for 1 to 2 minutes, with the vinegar providing the equivalent of the acetowhite staining that is used in cervical dysplasia screening. The anoscope is then reinserted for examination. Suspicious lesions, such as those with acetowhitening or areas showing punctation, mosaicism, atypical vessels, or ulcerations, should be biopsied (eg, with baby Tischler forceps). Lugol's iodine can be applied, causing dysplastic lesions to appear mustard or light yellow instead of mahogany brown.

Chin-Hong and Palefsky recently updated screening and treatment recommendations for anal HPV disease. Dr Mathews and colleagues perform high-resolution anoscopy in patients with ASCUS, LSIL, or HSIL. In patients with normal Pap findings, Pap testing may be repeated in 1 year in those with HIV infection and in 2 to 3 years in those without HIV infection. In patients with cytologic abnormalities whose initial high-resolution anoscopy-guided biopsy shows either no lesion or one of lesser severity than the Pap test, repeat high-resolution anoscopy is recommended at approximately 3 months. Patients with LSIL undergo repeat colposcopy at 6 months; those with HSIL or severe dysplasia or those with carcinoma in situ who do not undergo treatment have colposcopy repeated at 3 months.

Current estimates indicate that anal dysplasia screening would be highly

cost-effective. Typically, treatment modalities with a cost of less than \$30,000 to \$50,000 per year of life saved are considered cost-effective by policy makers. Cervical cytology screening every 3 years in HIV-seronegative women is estimated to have a cost-effectiveness ratio of approximately \$180,000 per year of life saved, compared with a ratio of approximately \$13,100 per life-year saved with annual screening in HIV-infected women (Goldie et al, *Ann Intern Med*, 1999; Eddy, *Ann Intern Med*, 1990). The cost per life-year saved with anal cytology screening is estimated at approximately \$11,000 for HIV-infected men with annual screening and approximately \$7800 for HIV-uninfected men with screening every 3 years (Goldie et al, *JAMA*, 1999; Goldie et al, *Am J Med*, 2000).

Does Screening Improve Treatment Outcome?

Unfortunately, there currently is no widely accepted standard of treatment for anal squamous intraepithelial lesions. One approach was recently proposed by Chin-Hong and Palefsky (*Clin Infect Dis*, 2002). Only those patients with HSIL should be routinely recommended for treatment. Treatment options are limited by morbidity and high (50%-85%) recurrence rates. Current options include excision with fulguration; topical treatment with 80% trichloroacetic acid, cryotherapy, imiquimod, podophyllotoxin, or 5-fluorouracil cream; laser ablation; thermo-coagulation or infrared coagulation; and intralesional interferon alfa. Immunologic therapies may ultimately offer the best hope of effective treatment.

Investigational Immunologic Therapies

One investigational vaccine, ZYC101a, is derived from a plasmid DNA encoding multiple HLA-A2-restricted cytotoxic T lymphocyte epitopes from the HPV-16 E7 protein. In a small study, 12 men with HPV-16 and the appropriate HLA-A2 restriction received 4 intramuscular injections of the vaccine 3 weeks apart. Enzyme-linked immunosorbent assay of peripheral blood mononuclear cells

from the subjects showed HPV-specific γ -interferon-producing cells in samples from each of the 9 who were evaluable for response (Lathey et al, 41st ICAAC, 2001). Also encouraging have been findings of a study of HspE7, a recombinant fusion product of the heat shock protein 65 and the E7 protein. Of 56 patients with anal HSIL receiving 3 500- μ g injections of the vaccine, 40 (71%) had dysplasia downgraded to LSIL at 6 months after immunization. Only 3 of 37 evaluated responders were HPV-16-positive, indicating a broad, non-type-specific response to the vaccine (Palefsky et al, 41st ICAAC, 2001).

Conclusions

Anal HSIL is likely a precursor to anal carcinoma. Anal dysplasia is detectable by Pap screening and colposcopic biopsy, but the relatively low reproducibility of the Pap testing results is a limiting characteristic in screening. Current treatment options for HSIL and carcinoma in situ are relatively ineffective, but monitoring may detect early invasive disease and permit better tolerance and outcome of treatment. There is some promise of better treatment alternatives in the near future. Until treatment improves, some form of screening for anal dysplasia is prudent, including 2 baseline Pap tests, routine digital rectal exam, and high-resolution anoscopy, if available.

Presented by Dr Mathews in November 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Mathews in January 2003.

Financial Disclosure: Dr Mathews has received grant and research support from Abbott, Agouron, and Gilead.

Suggested Reading

Chang GJ, Berry JM, Jay N, Palefsky JM, Welton ML. Surgical treatment of high-grade anal squamous intraepithelial lesions: a prospective study. *Dis Colon Rectum*. 2002;45:453-458.

Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus. *Clin Infect Dis*. 2002;35:1127-1134.

Daling JR, Weiss NS, Hislop TG, et al. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *N Engl J Med* 1987;317:973-977.

Eddy DM. Screening for cervical cancer. *Ann Intern Med* 1990;113:214-226.

Goedert JJ, Cote TR, Virgo P, et al. Spectrum of AIDS-associated malignant disorders. *Lancet*. 1998;351:1833-1839.

Goldie SJ, Kuntz KM, Weinstein B, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA*. 1999;281:1822-1829.

Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. *Am J Med*. 2000;108:634-641.

Goldie SJ, Weinstein MC, Kuntz KM, Freedberg KA. The costs, clinical benefits, and cost-effectiveness of screening for cervical cancer in HIV-infected women. *Ann Intern Med* 1999;130:97-107

Holly EA, Ralston ML, Darragh TM, Greenblatt RM, Jay N, Palefsky JM. Prevalence and risk factors for anal squamous intraepithelial lesions in women. *J Natl Cancer Inst*. 2001;93:843-849.

Jay N, Holly EA, Berry M, Hogeboom CJ, Darragh TM, Palefsky JM. Colposcopic correlates of anal squamous intraepithelial lesions. *Dis Colon Rectum*. 1997;40:919-928.

Lathey JL, Matijevic M, Klencke B, Palefsky J, Urban RG, Hedley ML. Immune responses are increased in ASIL patients following human papillomavirus (HPV) DNA immunization. [Abstract G-1564.] 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. September 22-25, 2001; Chicago, Illinois.

Mathews C, Mar-Tang M, Smith D, Saville W, Cosman B. Reproducibility and outcomes of anal dysplasia screening in an HIV primary care clinic. [Abstract 605-W.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.

Melbye M, Smith E, Wohlfahrt J, et al. Anal and cervical abnormality in women—prediction by human papillomavirus tests. *Int J Cancer*. 1996;68:559-564.

Minkoff H, Ahdieh L, Massad LS, et al. The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV-infected women. *AIDS*. 2001;15:2157-2164.

Östör AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol*. 1993;12:186-192.

Palefsky JM. Anal squamous intraepithelial lesions in human immunodeficiency virus-

positive men and women. *Semin Oncol.* 2000; 27:471-479.

Palefsky JM, Goldstone SE, Winnett M, Siegel MI, Neefe JR. HspE7 treatment of anal dysplasia: results of an open-label trial of HspE7 and comparison with a prior controlled trial of low dose HspE7. [Abstract H-1600.] 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. September 22-25, 2001; Chicago, Illinois.

Palefsky JM, Holly EA, Ralston ML, et al. Anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual and bisexual men: prevalence and risk factors. *J Acquir Immune*

Defic Syndr Hum Retrovirol. 1998;17:320-326.

Palefsky JM, Holly EA, Ralston ML, et al. Effect of highly active antiretroviral therapy on the natural history of anal squamous intraepithelial lesions and anal human papillomavirus infection. *J Acquir Immune Defic Syndr.* 2001;28:422-428.

Palefsky JM, Holly EA, Ralston ML, Jay N. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. *J Infect Dis.* 1998;177:361-367.

Solomon D, Davey D, Kurman R, et al. The 2001

Bethesda System: terminology for reporting results of cervical cytology. *JAMA.* 2002;287: 2114-2119.

Williams AB, Darragh TM, Vranizan K, Ochia C, Moss AR, Palefsky JM. Anal and cervical human papillomavirus infection and risk of anal and cervical epithelial abnormalities in human immunodeficiency virus-infected women. *Obstet Gynecol.* 1994;83:45-49.

Top HIV Med. 2003;11(2):45-49

Copyright © 2003 International AIDS Society–USA

IMPROVING THE MANAGEMENT OF HIV DISEASE®

Advanced CME Courses in

HIV PATHOGENESIS, ANTIRETROVIRALS, AND OTHER SELECTED ISSUES IN HIV DISEASE MANAGEMENT

This is the eleventh year of advanced CME courses designed for physicians who are actively involved in the care of patients with HIV disease. These programs offer a dynamic course agenda, with expert faculty speaking on timely and clinically relevant issues in HIV disease management.

This course series is made possible through educational grants from commercial companies that are committed to supporting CME in the field of HIV/AIDS:

Major Grant Support

These companies have continuously supported this program at the major grant support level since its inception 11 years ago.

Bristol-Myers Squibb Co.

GlaxoSmithKline

Roche Laboratories/Trimeris, Inc.

Substantial Grant Support

Abbott Laboratories

Agouron Pharmaceuticals, Inc.

Generous Grant Support

Boehringer Ingelheim Pharmaceuticals, Inc.

Gilead Sciences, Inc.

Merck US Human Health

Ortho Biotech Products, L.P.

Mark Your Calendar!

LOS ANGELES, CALIFORNIA

Saturday, March 8, 2003

Los Angeles Marriott Downtown

ATLANTA, GEORGIA

Thursday, March 20, 2003

Westin Peachtree Plaza

NEW YORK, NEW YORK

Friday, March 28, 2003

Hilton New York

CHICAGO, ILLINOIS

Thursday, April 24, 2003

Hyatt Regency McCormick Place

SAN FRANCISCO, CALIFORNIA

Tuesday, May 6, 2003

Hotel Nikko San Francisco

WASHINGTON, DC

Tuesday, May 20, 2003

Marriott at Metro Center

Please visit our Web site

www.iasusa.org

for course updates and registration information.

Phone: (415) 544-9400 Fax: (415) 544-9402

E-mail: cme@iasusa.org