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Correspondence and requests for reprints should be addressed to Cullen M. Dutmer, M.D., 13123 East 16th Avenue, Box 518, Aurora, CO 80045. E-mail: [cullen.dutmer@childrenscolorado.org](mailto:cullen.dutmer@childrenscolorado.org).

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## Chronic Obstructive Pulmonary Disease and Herbicide Exposure in Vietnam-Era U.S. Army Chemical Corps Veterans

Yasmin Cypel<sup>1</sup>, Stella E. Hines<sup>2</sup>, Victoria J. Davey<sup>3</sup>,  
Stephanie M. Eber<sup>1</sup>, and Aaron I. Schneiderman<sup>1</sup>

<sup>1</sup>Epidemiology Program, Post-Deployment Health Services (10P4Q), Office of Patient Care Services, and <sup>3</sup>Office of Research and Development, Department of Veterans Affairs, Washington, District of Columbia; and <sup>2</sup>University of Maryland–Baltimore School of Medicine, Baltimore, Maryland

**Rationale:** Past research demonstrates a possible association between herbicide exposure and respiratory health. Biologic plausibility and inhalation as a mode of exposure further support the contention that herbicides may act as adverse contributors to respiratory status, especially in military personnel who were responsible for chemical maintenance and distribution during the Vietnam War.

**Objectives:** This study examines the association between chronic obstructive pulmonary disease and herbicide exposure among Vietnam-era U.S. Army Chemical Corps veterans.

**Methods:** A 2013 three-phase health study was conducted that included a survey (mail or telephone), in-home physical examinations, and medical record reviews/abstractions. Living, eligible veterans ( $n = 4,027$ ) were identified using an existing cohort of men ( $n = 5,609$ ) who either served in Vietnam ( $n = 2,872$ ) or never served in Southeast Asia ( $n = 2,737$ ). The health survey collected self-reported data on physician-diagnosed pulmonary conditions (chronic obstructive pulmonary disease, emphysema, and chronic bronchitis), service-related herbicide spraying history, cigarette smoking status, alcohol use, and demographics. Data from service personnel files confirmed chemical operations involvement and service status, whereas serum samples analyzed for 2,3,7,8-tetrachlorodibenzo-p-dioxin supported self-reported herbicide exposure. National Institute for Occupational Safety and Health quality-assured spirometry was performed during the physical examinations on a subset of survey respondents ( $n = 468$  of 733 selected for participation and who provided consent) to determine mainly spirometric obstructive respiratory disease (forced expiratory volume in 1 second [FEV<sub>1</sub>]/forced vital capacity [FVC] < lower limit of normal [LLN], FVC ≥ LLN, and FEV<sub>1</sub> < LLN; and FEV<sub>1</sub>/FVC < LLN and FEV<sub>1</sub> ≥ LLN). Associations between chronic obstructive pulmonary disease and veteran characteristics were examined ( $n = 403$ ) using multivariable models.

**Results:** Reporting here specifically on spirometrically diagnosed disease, prevalence of obstructive disease was 8.4%. No significant differences in mean values of FEV<sub>1</sub>/FVC or mean percentage of predicted for FEV<sub>1</sub> and FVC between herbicide sprayers and nonsprayers were found. The odds of spirometric obstructive disease among sprayers were 0.65 times the odds among nonsprayers (adjusted odds ratio, 0.65; 95% confidence interval, 0.28–1.47), although elevated odds for spirometric restrictive disease were observed for sprayers versus nonsprayers (adjusted odds ratio, 1.61; 95% confidence interval, 0.85–3.06). Race/ethnicity, anthropometric measures, and cigarette smoking status accounted for differences among veterans' respiratory patterns.

**Conclusions:** No significant association between herbicide exposure and spirometry-determined chronic obstructive pulmonary disease was found. Greater focus is required on confirming diagnoses of respiratory disease through spirometry in epidemiological research.

**Keywords:** herbicides; chronic obstructive pulmonary disease; Vietnam War

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Correspondence and requests for reprints should be addressed to Yasmin Cypel, Ph.D., M.S., Epidemiology Program, Post-Deployment Health Services (10P4Q), Office of Patient Care Services, 810 Vermont Avenue, NW, U.S. Department of Veterans Affairs, Washington, DC 20420. E-mail: [yasmin.cypel@va.gov](mailto:yasmin.cypel@va.gov).

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## Effects of Household Air Pollution in Malawi and Human Immunodeficiency Virus Status on Respiratory Symptoms and Inflammation, Injury, and Repair Markers

Charles Kim<sup>1</sup>, Hannah Jary<sup>2,3</sup>, Kevin Mortimer<sup>3</sup>,  
Kelly S. Schweitzer<sup>4</sup>, Doug Curran-Everett<sup>1,4</sup>, Stephen Gordon<sup>5</sup>,  
and Irina Petrache<sup>1,4</sup>

<sup>1</sup>University of Colorado Denver, Anschutz Medical Campus, Aurora, Colorado; <sup>2</sup>Wellcome Trust Tropical Centre, University of Liverpool, Liverpool, United Kingdom; <sup>3</sup>Malawi Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi; <sup>4</sup>National Jewish Health, Denver, Colorado; and <sup>5</sup>Liverpool School of Tropical Medicine, University of Liverpool, Liverpool, United Kingdom

**Rationale:** Household air pollution (HAP) and human immunodeficiency virus (HIV) are associated with increased risk for chronic obstructive pulmonary disease. Both HAP and HIV are widespread in Sub-Saharan Africa, including Malawi, where HIV has 10.6% prevalence in patients 15–49 years old.

**Objectives:** We hypothesized that HIV infection (HIV<sup>+</sup>) and habitual exposure to HAP (HAP<sup>+</sup>) synergize to cause systemic inflammation and vascular injury, which may herald early onset of chronic respiratory diseases.

**Methods:** In this pilot study, 50 subjects from Malawi with known HIV status were administered surveys recording demographics, HAP exposure, and respiratory symptoms/diagnoses. Peripheral blood was collected, and Meso Scale Discovery V-Plex assay was used to measure the levels of 41 serum markers.

**Results:** Almost all subjects (96%) reported HAP<sup>+</sup>, 30 were HIV<sup>+</sup>, 20 were HIV<sup>-</sup>, with a mean age of 22 years in both groups. More females (73%) were HIV<sup>+</sup>, whereas 65% of those who were HIV<sup>-</sup> were males. The vast majority were never-smokers (70% of HIV<sup>-</sup> and 83% of HIV<sup>+</sup> subjects, respectively). Forty-six percent of all subjects (57% of HIV<sup>+</sup>HAP<sup>+</sup> and 33% of HIV<sup>-</sup>HAP<sup>+</sup>) reported respiratory diagnoses and/or respiratory symptoms, with breathlessness and cough being most common. Although HIV<sup>+</sup>HAP<sup>+</sup> individuals had a trend to increased proinflammatory cytokines and vascular injury markers, and decreases in proangiogenic factors compared with HIV<sup>-</sup>HAP<sup>+</sup>, only the decrease in serum interleukin-16 (by 44%) was statistically significant ( $P = 0.03$ ). Also, compared with other subjects, serum interleukin-2 levels were significantly decreased (by 31%;  $P = 0.02$ ) in HIV<sup>+</sup> subjects with persistent respiratory symptoms.

**Conclusions:** This study suggests a high prevalence of respiratory symptoms in HIV<sup>+</sup> individuals exposed to HAP. The significant decrease in interleukin-2 and interleukin-16, cytokines associated with HIV clearance, may contribute to viral persistence, and because their low levels were found to correlate with chronic obstructive pulmonary disease severity, they may serve as biomarkers for risk of chronic obstructive pulmonary disease in this vulnerable population.

**Keywords:** HIV; chronic obstructive pulmonary disease; indoor air pollution; household air pollution; Malawi

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Correspondence and requests for reprints should be addressed to Charles Kim, M.D., University of Colorado Denver School of Medicine, Internal Medicine, 5955 E. 10th Ave., Apt. 510, Aurora, CO. Email: [charles.kim@ucdenver.edu](mailto:charles.kim@ucdenver.edu).

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## A Pilot Study Assessing the Ability of 5-Aminosalicylic Acid to Modulate the Immune Response in Chronic Beryllium Disease

Brian J. Day<sup>1,2,3,4,5</sup>, Jie Huang<sup>1</sup>, Briana Q. Barkes<sup>1</sup>,  
May Gillespie<sup>1</sup>, Li Li<sup>1</sup>, and Lisa A. Maier<sup>1,2,4</sup>

<sup>1</sup>Division of Environmental and Occupational Health Sciences, Hollis Laboratory, Department of Medicine, National Jewish Health, Denver, Colorado; and <sup>2</sup>Department of Medicine; <sup>3</sup>Department of Immunology and Microbiology; <sup>4</sup>Department of Environmental Health Sciences, and <sup>5</sup>Department of Pharmaceutical Sciences, University of Colorado at Denver, Aurora, Colorado

Chronic beryllium disease is a granulomatous lung disease, characterized by the accumulation of macrophages and beryllium-specific CD4<sup>+</sup> T-cells that proliferate and produce T-helper cell type 1 cytokines. Previous studies indicate that beryllium-mediated oxidative stress enhances cytokine response in chronic beryllium disease CD4<sup>+</sup> T-cells. 5-Aminosalicylic acid (5-ASA) is currently used to treat inflammatory bowel disease and has both antioxidant and antiinflammatory actions. We hypothesized that 5-ASA therapy may be a beneficial therapy in chronic beryllium disease. An investigator-initiated, randomized, double-blind, placebo-controlled 5-ASA trial was undertaken. Patients with chronic beryllium disease were randomized 3:1 to receive 5-ASA (500-mg capsules) four times daily ( $n = 13$ ) or placebo capsules ( $n = 5$ ), for 6 weeks. Primary study endpoints included changes in beryllium lymphocyte proliferation test responses in peripheral blood mononuclear cells and bronchoalveolar lavage cells. Secondary endpoints included changes in bronchoalveolar lavage fluid cells, serum, and peripheral blood mononuclear cell glutathione levels, bronchoalveolar lavage cell-stimulated tumor necrosis factor- $\alpha$  levels, lung function, and quality of life as measured by the Short Form 36 questionnaire. 5-ASA decreased bronchoalveolar lavage cell beryllium lymphocyte proliferation test responses by 20% within the 5-ASA treatment group ( $P = 0.06$ ), although this was not seen for blood beryllium lymphocyte proliferation test responses. No significant changes were observed in serum, peripheral blood mononuclear cells, bronchoalveolar lavage fluid, or bronchoalveolar lavage cell glutathione levels in either the 5-ASA or placebo treatment group. 5-ASA treatment decreased *ex vivo* beryllium-stimulated bronchoalveolar lavage cell tumor necrosis factor- $\alpha$  levels within the 5-ASA group ( $P = 0.06$ ) and when compared with placebo ( $P = 0.04$ ). Significant improvements were noted in quality of life measurements with 5-ASA treatment. The ability of 5-ASA to decrease bronchoalveolar lavage cell beryllium lymphocyte proliferation test responses and diminish beryllium-stimulated bronchoalveolar lavage cell tumor necrosis factor- $\alpha$  levels suggests that 5-ASA may impact the beryllium-specific immune response in chronic beryllium disease.

Clinical trial registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01088243).

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Correspondence and requests for reprints should be addressed to Brian J. Day, Ph.D., National Jewish Health, Medicine, 1400 Jackson Street, Denver, CO 80206. E-mail: [dayb@njhealth.org](mailto:dayb@njhealth.org).

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