Benefits and Harms of Lung Cancer Screening in HIV Infection

SPECIFIC AIMS

Lung cancer is the most common non-AIDS defining cancer (NADC) and leading source of NADC mortality amongst HIV infected (HIV+) individuals.\textsuperscript{1,2} HIV+ persons have an increased burden of lung cancer due to higher smoking rates combined with an independent HIV related increased risk of lung cancer.\textsuperscript{1,3-12} Unfortunately, most lung cancers are clinically diagnosed at an advanced stage and have 5-year survival rates <15%. Earlier detection strategies to improve lung cancer mortality among HIV+ persons are urgently needed.

Recently, the National Lung Screening Trial (NLST) demonstrated that low-dose screening chest computed tomography (CT) led to a 20% reduction in lung cancer mortality among high-risk, HIV uninfected (HIV-) smokers.\textsuperscript{13} As a result, lung cancer screening was recently recommended by the National Comprehensive Cancer Network (NCCN),\textsuperscript{14} is covered by certain large insurance companies\textsuperscript{15} and is anticipated to become standard of care. Extrapolating results of the NLST to HIV+ individuals is challenging. The increased risk and burden of lung cancer in this aging population would make HIV+ persons excellent candidates for screening. However, HIV+ persons also experience considerable multimorbidity and can have higher mortality from competing risks. Thus, how to apply results of the NLST to HIV+ persons is unclear, as some patients may not survive long enough to derive benefits of screening. Additionally, HIV+ persons may be more likely to have false positive CT scans due to prior lung disease and immunocompromise. Consequently, the morbidity associated with the work-up of benign nodules, which are quite common, could be significant.

Given that an RCT limited to HIV+ patients is very unlikely in the near future, we propose to develop a mathematical model that estimates the potential benefits of screening, identifies the appropriate candidates for screening, and determines the best screening regimen. As the health care burden of screening CT can be substantial, we will first determine the clinical consequences that result from performing screening chest CT scans among HIV+ individuals by analyzing results of CT scans and data from a large cohort study (Lung HIV Study).\textsuperscript{16} Then, we will construct a model to estimate the impact of lung cancer screening on mortality among HIV+ persons; we will compare this model and its results to one generated by our collaborators in the NCI-funded Cancer Intervention and Surveillance Modeling Network (CISNET). We will determine the mortality benefit in different HIV+ populations, considering the optimal regimen and age for screening, as we hypothesize that HIV+ persons will benefit from starting and stopping screening at younger ages compared to HIV- high risk smokers. In addition to synthesis of published literature, we will determine incidence rates and complications of lung cancer evaluation and treatment, and competing risks of mortality from other causes to inform our model, using data from the Veterans Aging Cohort Study\textsuperscript{17} that includes a Virtual Cohort\textsuperscript{18} of >44,000 HIV+ persons and a prospective cohort of >3,500 HIV+ persons, as well as the >22,000 person Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) Study.\textsuperscript{19}

We have assembled a multi-disciplinary group of investigators, with expertise in HIV associated lung diseases and observational data analysis (Dr. Crothers); mathematical modeling and operations research (Dr. Braithwaite); and lung cancer and screening (Dr. Wisnivesky). We propose the following aims and hypotheses:

**Aim 1. Determine the frequency and sequelae of work-up of non-calcified nodules (NCNs) and other abnormal findings on chest CT scans in HIV+ persons, and compare results to HIV- persons.**

\textbf{H1a:} The probability of a NCN or other abnormal finding is greater in HIV+ compared to HIV- persons.

\textbf{H1b.} Predictors of NCNs among HIV+ persons include chronic obstructive pulmonary disease (COPD), prior opportunistic pulmonary infection, and greater immunocompromise, as reflected by lower CD4 cell count.

\textbf{H1c.} HIV+ persons are more likely than HIV- persons to undergo additional studies if NCNs or other abnormalities are detected on chest CT.

**Aim 2. Develop and validate a mathematical model of lung cancer screening, explicitly considering HIV and comorbidity-attributable differences in benefits and harms.**

\textbf{H2a:} The model can accurately individualize the benefits and harms of screening among HIV+ persons.

**Aim 3. Estimate the potential mortality benefit of screening among HIV+ persons and determine the optimal lung cancer screening regimen, considering age at initiation and duration of screening.**

\textbf{H3a.} Lung cancer screening confers mortality benefit for well-controlled, otherwise healthy HIV+ smokers.

\textbf{H3b.} Increased morbidity (poorly controlled HIV infection, severe comorbid diseases or abnormalities in laboratory biomarkers reflecting end-organ injury) attenuates the benefit of lung cancer screening.

\textbf{H3c.} Optimal benefit occurs with starting and stopping screening at younger ages in HIV+ persons.