Global Considerations in HIV-associated Respiratory Disease

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# Abstract

Respiratory tract infection, particularly tuberculosis, is a major cause of mortality among HIV-infected individuals. Antiretroviral therapy has resulted in a dramatic increase in survival, although coverage of HIV treatment remains low in many parts of the world. There is a concurrent growing burden of chronic non-infectious respiratory disease as a result of increased survival. Many risk factors associated with development of respiratory disease such as cigarette smoking and intravenous drug use are over-represented among people living with HIV. In addition, there is emerging evidence that HIV may directly cause or accelerate the course of chronic lung disease. This review summarises the clinical spectrum and epidemiology of respiratory tract infections and non-infectious pulmonary pathologies, and factors that explain the global variation in HIV-associated respiratory disease. The potential for enhancing diagnoses of non-infective chronic conditions through the use of clinical algorithms is discussed. We also consider issues in assessment and management of HIV-related respiratory disease in view of the increasing global scale-up of ART.

# ****Keywords****

**Lung, HIV, Respiratory tract Infection, Chronic lung disease, Developing Countries, Algorithms**

# Introduction

Over 36 million adults and children were living with Human Immunodeficiency Virus (HIV) infection by the end of 2014 and globally HIV infection ranks as the 6thleading cause of mortality.[1](#_ENREF_1),[2](#_ENREF_2) The burden of HIV infection falls disproportionately on low and middle income countries (LMIC): two thirds of HIV-infected people live in sub-Saharan Africa, and globally 15 countries account for nearly 75% of all people living with HIV.[3](#_ENREF_3)

The scale-up of antiretroviral therapy (ART) in LMIC has resulted in a dramatic increase in survival of HIV-infected adults, but lung diseases remain a major contributor to mortality in both HIV-infected adults and children.[4](#_ENREF_4),[5](#_ENREF_5) Respiratory tract infections (RTI) are a common manifestation of immunosuppression caused by HIV infection, especially in settings where combination ART coverage is low. In addition, there has been a concurrent increase in the burden of chronic lung disease (CLD) particularly as people live longer due to effective viral suppression.[6](#_ENREF_6) Risk factors associated with development of CLD such as cigarette smoking and injection drug use may be over-represented in HIV-infected individuals, and recurrent RTIs and tuberculosis may themselves cause lung damage.[7](#_ENREF_7),[8](#_ENREF_8) There is increasing evidence of HIV directly causing organ damage, mainly through dysregulated chronic immune activation, which may impact on development or progression of pulmonary pathology.[9](#_ENREF_9),[10](#_ENREF_10)

We review the spectrum of respiratory disease in the context of HIV infection, factors that influence the epidemiology of respiratory disease and global considerations in assessment and management of HIV-related respiratory disease.

# Spectrum of HIV-related respiratory disease

HIV infection results in immunosuppression which increases the risk of infection of the respiratory tract with bacteria, fungal, and viral pathogens. Chronic lung damage can occur as sequelae of these infections.

## Respiratory tract infections

HIV infection increases the incidence of severe acute respiratory tract infection (RTI) across all age-groups. Prospective surveillance data from sub-Saharan Africa and high income countries consistently show a higher incidence of severe all-cause acute RTI or pneumonia in HIV-infected compared to uninfected adults and children.[11-15](#_ENREF_11) Risk factors for RTIs among HIV-infected individuals include increasing age, greater immunosuppression, recurrent pneumonia, and cigarette smoking.[16](#_ENREF_16) In LMIC, these risks are compounded by other factors such as poor hygiene, and unreliable water supplies.[17](#_ENREF_17) The increased risk of pneumonia in HIV-infected adults is independent of previous tuberculosis (TB) and chronic lung scarring amongst mining populations in South Africa.[18](#_ENREF_18) However, population rates of acute RTI in HIV-infected individuals vary widely between studies in Asia, sub-Saharan Africa, and high-income countries, and may reflect different approaches to diagnosis and health seeking behaviour, in addition to true variation in incidence.[19-22](#_ENREF_19)

HIV infected adults hospitalised with community acquired pneumonia in resource rich settings appear to have higher mortality than non-infected individuals. However, after adjusting for comorbidities and confounders, per-episode mortality outcomes are similar.[23](#_ENREF_23),[24](#_ENREF_24) Data from adults in LMIC are similarly mixed. Some studies demonstrate an association between HIV infection and mortality amongst adults hospitalised with all-cause pneumonia, whilst others have not shown this relationship.[21](#_ENREF_21),[25](#_ENREF_25) In contrast, meta-analysis has shown that HIV-infected children suffer higher odds of hospitalisation and death compared with uninfected children. Modelling estimates suggest that 60% of all paediatric pneumonia deaths occurring in HIV-infected children.[26](#_ENREF_26) The majority of included studies on which the model was based were conducted in the pre-ART era: the impact of ART on these outcomes could not be determined.

Identification of pathogens responsible for respiratory infections is challenging in all settings, but particularly difficult in LMIC where invasive investigations and diagnostic services such as culture and PCR are not readily available. However, it is widely held that bacterial pathogens causing respiratory infection are similar in HIV-infected and uninfected individuals.[24](#_ENREF_24),[27](#_ENREF_27) In resource rich settings the dominant organisms causing pneumonia in HIV-infected adults include *Streptococcus pneumoni*ae, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella*, and *Haemophilus influenzae.*[28](#_ENREF_28) *Streptococcus pneumoniae* is also the most common pathogen in LMIC.[25](#_ENREF_25) However, the spectrum and relative importance of pathogens depends on the local context and pathogen endemicity: a review from Asia suggested that Gram-negative bacteria and *Staphylococcus aureus* are more commonly identified causes of community acquired pneumonia that in resource rich settings.[29](#_ENREF_29) Another example is melioidosis caused by *Burkholderia pseudomallei*, which is endemic to regions of Asia and Australia. This infection can present as pneumonia, acute fulminant sepsis, or chronic infection mimicking TB. Melioidosis must therefore be considered in the design of empirical antibiotic regimens for both HIV-infected and uninfected groups in these settings.[30](#_ENREF_30)

Data on the global epidemiology of viral respiratory tract infections, including influenza, has emerged only in recent years. Influenza is common in resource-poor settings where it is thought to cause between 5% and 27% of all severe respiratory tract infections.[31](#_ENREF_31) During the 2009 H1N1 epidemic in South Africa, individuals with HIV accounted for 20% of deaths compared with a 10% population prevalence of HIV. Bacterial infection was more common in HIV-infected individuals, and affected individuals suffered greater degrees of breathlessness (a surrogate marker for severity).[32](#_ENREF_32) Other viral pathogens including respiratory syncytial virus are commonly seen in HIV-infected children hospitalised with RTI; these have been associated with poor outcomes, and higher risk of developing obliterative bronchiolitis.[33-36](#_ENREF_33)

People living with HIV are at high risk of developing tuberculosis (TB), with a median global incidence rate ratio of 29 (range 26-31) compared with the HIV-uninfected population. In 2013, 1.1 million of the 9.0 million worldwide cases of TB disease were HIV-infected, of which 78% occurred in the African region.[37](#_ENREF_37) Diagnosis of TB disease among HIV-infected individuals is difficult, even at higher CD4 counts. Extrapulmonary and disseminated disease patterns are more common, and a higher proportion of pulmonary disease is smear-negative.[38](#_ENREF_38) Pulmonary disease is also less easy to identify on chest radiography because there is less cavitation and disease may not be confined to the upper lobes as is typical in immunocompetent adults.[39](#_ENREF_39) Mortality in HIV-TB co-infected patients is high in both resource-rich and resource-limited settings. Up to 25% of HIV-associated deaths globally are thought to be related to TB disease.[40-45](#_ENREF_40) Bacterial superinfection and disseminated TB disease are frequent in LMIC, and post-mortem studies suggest that up to 50% of TB disease remains undiagnosed in these settings, even in the post-ART era.[5](#_ENREF_5),[46-49](#_ENREF_46) Treatment of HIV-TB co-infected patients is complicated by the risk of immune reconstitution syndrome (IRIS), and pharmacokinetic interactions and overlapping toxicities between ART and TB drugs, particularly when second line or multi-drug resistance regimens are required.[50](#_ENREF_50),[51](#_ENREF_51)

Opportunistic infections pose additional risk with increasing immunosuppression. *Pneumocystis jirovecii* pneumonia (PCP) is the one of the most common opportunistic infections associated with HIV infection, but appears to be less common in resource-limited settings. Although it is a ubiquitous pathogen, a recent review of risk factors for PCP in LMIC included 33 studies from Africa, Asia and the Americas, and confirmed a 10 times higher PCP incidence in countries with a high per-capita gross domestic product compared to the poorest countries. This relationship persisted after adjusting for differences in diagnostic accuracy, and when analysis was restricted to include only high quality diagnostic tests.[52](#_ENREF_52) These findings are supported by the low PCP prevalence seen in other autopsy and clinical studies from LMIC.[5](#_ENREF_5) The case fatality in LMIC is higher: the same study estimated mortality to be 30.9%, compared with 8.4% in a US cohort.[53](#_ENREF_53) This difference may relate to the high rate of co-infection with TB, CMV, and bacteria, but the limitations of clinical care in LMIC are likely to be responsible for some of this discrepancy.

*Cryptococcus neoformans* is found worldwide resulting in disseminated disease in severely immunocompromised individuals. Pulmonary involvement occurs in up to half of patients, but has a non-specific clinical presentation and diverse appearances on radiological imaging.[54](#_ENREF_54) The clinical index of suspicion for pulmonary cryptococcal infection should be higher in the presence of skin lesions, or signs of meningitis. While cryptococcal disease incidence is falling in resource-rich settings with high rates of ART provision, it remains common and often fatal in LMIC.[55](#_ENREF_55)

Unlike Cryptococcus, *Histoplasma capsulatum* is more geographically limited. HIV-related histoplasmosis appears most common in South America, but it has been documented in parts of North and Central America, Africa, Asia and Australia. HIV-infected individuals suffer disseminated disease, although respiratory symptoms which occur in less than 50% can mimic advanced tuberculous disease. Diagnostic sensitivity of antigen detection of histoplasmosis in BAL is high, but access to bronchoscopy services remains limited in many LMIC.[56](#_ENREF_56) Prospective cohort study of HIV-infected individuals in French Guinea has estimated the incidence of disseminated histoplasmosis to be 15.4/1000 person years.[57](#_ENREF_57) Mortality in endemic areas is thought to be 10%, but this can be higher in low prevalence areas where there recognition of disease may be delayed.[58](#_ENREF_58)

## Chronic respiratory disease

In cohorts from the US, high rates of ART provision now means that diseases of aging are prominent: there is a concurrent rise in the burden of chronic pulmonary disease, including airway, parenchymal and pulmonary vascular disease.[59](#_ENREF_59) Economic transition of LMIC, and the extensive availability and early initiation of ART, are likely to mean chronic conditions become proportionally more important than infectious disease in these settings. Mechanisms underlying these chronic diseases include the direct HIV-related immune activation and inflammation on the lung, which may be compounded by the sequelae of TB or recurrent RTIs, inhaled toxins, biomass fuels and smoking. The relative population attributable fraction for each of these risk factors will vary globally.

Studies from high income countries suggest that the prevalence of chronic obstructive pulmonary disease (COPD) is higher in HIV-infected than HIV-uninfected adults. After controlling for confounders such as cigarette smoking and substance use, there is an increased odds of obstructive spirometry, with lower FEV1, FVC, and gas transfer.[60](#_ENREF_60),[61](#_ENREF_61) FEV1 declines faster in HIV-infected individuals with COPD, hypothesised to be due to the dysregulated immune activation, or a consequence of pulmonary co-infections.[62-65](#_ENREF_62) The Burden of Obstructive Lung Disease (BOLD) project, an international cross sectional study of adults age ≥40 years, provides data on COPD burden in LMIC.[66](#_ENREF_66) Spirometry-determined COPD prevalence in Cape Town, South Africa was 23.8%. This is significantly higher than that seen in resource-rich settings, and is consistent with subsequent studies in Africa, India, and SE Asia.[67-70](#_ENREF_67) Higher odds of COPD in HIV-infected compared to uninfected adults have also been demonstrated in case-control studies of Japanese men and Cameroonian adults.[71](#_ENREF_71),[72](#_ENREF_72) However, these studies were small, and reported high rates of biomass fuel exposure and self-reported previous TB. Such potential confounding makes the direct relationship between HIV infection and airway obstruction difficult to assess.

Chronic airway obstruction may also arise from bronchiectasis, tuberculosis and recurrent bacterial and viral respiratory infections. Bronchiectasis results in loss of lung function and in an increased risk of recurrent bacterial infections.[73](#_ENREF_73) In two studies cross-sectional studies of HIV infected adults on ART conducted in USA and Italy, the prevalence of computed tomography (CT) confirmed bronchiectasis was 10.7% and 16.7% respectively.[74](#_ENREF_74),[75](#_ENREF_75) Up to 90% of patients with bronchiectasis report chronic cough and many have chronic sputum production.[76](#_ENREF_76) In low-income settings where TB diagnostics and CT are not readily available, these symptoms therefore often result in a misdiagnosis of tuberculosis and unnecessary empirical TB treatment. particularly in children, who tend to have non-specific abnormalities on chest radiography.[77](#_ENREF_77)

Given the high burden of recurrent early childhood infections, bronchiectasis is an important cause of chronic lung disease in HIV-infected children.[78](#_ENREF_78),[79](#_ENREF_79) Recent studies from Southern Africa report chronic respiratory symptoms, predominantly longstanding cough and reduced exercise tolerance, in nearly a third of HIV-infected children accessing HIV care and treatment.[80](#_ENREF_80),[81](#_ENREF_81) A study from South Africa reports common and severe changes on chest radiography which improve on ART.[82](#_ENREF_82) However, high resolution CT findings in a Zimbabwean cohort are suggestive of obliterative bronchiolitis, often co-existing with bronchiectasis which are not likely to resolve.[83](#_ENREF_83),[84](#_ENREF_84) This pattern of lung disease has not previously been associated with paediatric HIV in low or high-income settings perhaps due to the lack of availability of CT. An explanation for the finding of obliterative bronchiolitis is unclear, but may be a result of the effect of childhood exposures such as malnutrition and recurrent viral and/or bacterial respiratory infections which are more prevalent in low-resource settings.[85](#_ENREF_85)

In addition to airway pathology, HIV-infection has been associated with parenchymal damage. Interstitial lung diseases documented in HIV-infected populations include non-specific interstitial pneumonitis, lymphocytic interstitial pneumonitis (LIP), cryptogenic organising pneumonia, and hypersensitivity pneumonitis, either directly related to HIV infection or to ART.[86](#_ENREF_86) The combined effect of occupational exposures and HIV-infection on the lung parenchyma is particularly important in LMIC given the number of migrant labourers with significant respiratory exposures. A key example is silicosis. In miners in South African, Indian and China, silicosis has been shown to have a multiplicative effect, together with HIV, as a risk factor for pulmonary TB.[87](#_ENREF_87) [88](#_ENREF_88) In the pre-ART era LIP was the leading cause of chronic lung disease in children, prevalent in 30-40% of HIV-infected children in both high-income and LMIC settings. LIP responds well to ART and its incidence has declined significantly with the availability of ART.[89](#_ENREF_89),[90](#_ENREF_90)

Lastly, the pulmonary vasculature is known to be affected by HIV-infection, either as a consequence of severe chronic respiratory disease (secondary pulmonary arterial hypertension [PAH]), or due to direct damage (primary PAH). The prevalence of PAH in HIV-infected resource rich cohorts is estimated at 0.1-2%, and as with HIV associated airway pathology, potential aetiologies include direct HIV-related immune activation and inflammation, pathogen co-infection, and risk-behaviours such as drug use that are prevalent in HIV-infected groups in these settings.[91](#_ENREF_91) Prevalence estimates from resource-poor settings have been based on the presence of elevated estimated pulmonary artery systolic pressures (ePASP) on Doppler echocardiography. Data from HIV-infected patients admitted to hospital in Zimbabwe and outpatient clinic attenders in Nigeria showed similar prevalence of 0.5% and 0.1% respectively, and a cross-sectional study of HIV-infected outpatients in India showed a prevalence of 3%.[92](#_ENREF_92),[93](#_ENREF_93)[94](#_ENREF_94) The challenge in measuring ePASP in resource-poor settings was documented in a large multisite study of echocardiographically-determined cardiac structure and function among HIV-infected adults in China, where this data was available from only 14% of patients.[95](#_ENREF_95) Additionally, differentiating between primary and secondary PAH can be difficult in resource-limited settings where potential for diagnosis of chronic lung disease is limited.[96](#_ENREF_96)

## Lung malignancy

The spectrum of intra-thoracic HIV-related malignancies appears to be similar in resource-poor and rich settings, and includes pulmonary Kaposi sarcoma (KS) and pulmonary lymphoma.[97-101](#_ENREF_97) Data on the relationship between HIV and bronchopulmonary lung cancer, are heavily confounded by exposures such as cigarette smoking and drug use. However, there is a clear excess of lung cancer in the Veterans Aging Cohort Study, and it appears likely that HIV-infection is a direct risk factor for these malignancies.[59](#_ENREF_59),[98](#_ENREF_98),[102](#_ENREF_102) Measurement of the prevalence and incidence of pulmonary malignancy in resource-poor settings is challenging: these are relatively rare events for which large cohorts or case-control analyses are required, and the comprehensive cancer registries that have provided much data in resource-rich settings are not widely available in LMIC.[103](#_ENREF_103) In addition, complex imaging and histopathology are required to make diagnoses, and neither are easily accessed in resource-poor environments. Although the incidence of AIDS-defining malignancies such as KS and lymphoma have declined in the post-ART era, no such change has been documented in the non-AIDS defining lung cancers.[104](#_ENREF_104)

# Global variation in the epidemiology of HIV-associated lung disease

The spectrum and severity of HIV-related lung disease varies worldwide. The interaction between environmental risk factors and HIV infection are likely to influence the risk and natural history of pulmonary disease, but are not well-understood. In addition, clinical outcomes will be influenced by capacity of health systems to prevent, diagnose and manage disease (Figure 1).

## Coverage of HIV treatment

There has been remarkable scale-up of ART globally, but coverage varies within and between regions. Access to ART in LMIC has improved resulting in a significant impact on life expectancies, but in LMIC only 34% (95%CI 32-37%) of those eligible for ART were receiving treatment according to WHO 2013 guidelines.[4](#_ENREF_4),[105](#_ENREF_105) In addition, the prevalence of HIV among women of childbearing age remains high in these countries. While significant advances have been made in services to prevent mother-to-child transmission (PMTCT), coverage of PMTCT programs and early infant diagnosis remains suboptimal so that children continue to be infected with HIV and may only be identified in late childhood.[3](#_ENREF_3),[106](#_ENREF_106)

Delayed diagnosis leads to development of chronic lung disease.[83](#_ENREF_83) The recent START and TEMPRANO examined the effect of immediate ART when presenting CD4 count exceeded 500 cells/mm3 compared with groups in which ART was deferred until patients met WHO criteria for ART. These studies found lower rates of mortality and severe illness in patients receiving immediate ART, and strongly support calls for earlier initiation of therapy.[107](#_ENREF_107),[108](#_ENREF_108) However, linkage to HIV care services and subsequent adherence are key determinants to successful clinical outcomes of ART. Health seeking behaviours affect the stage at which individuals with HIV infection present to healthcare services, and may alter the clinical stage at which a diagnosis is made. Such behaviours are culturally very diverse, but are commonly influenced by: distance to travel for care; low levels of education / literacy; symptom burden; cultural and lay beliefs about the cause of illness; direct costs of treatment; indirect financial constraints such as loss of earnings associated with treatment; family and community influences.[109](#_ENREF_109),[110](#_ENREF_110) These factors result in individuals being more profoundly immunosuppressed at presentation. Opportunistic infections are therefore more prominent and continue to represent a significant burden on healthcare systems in LMIC.[111](#_ENREF_111),[112](#_ENREF_112)

## Early life events and nutrition

Early nutritional deprivation is more frequent in LMIC, and is recognised to result in long-term consequences for adult disease profiles.[113](#_ENREF_113) For example, metabolic adaptations of the “thrifty phenotype”, HIV infection itself and ART are risk factors for the development of cardiovascular disease.[114](#_ENREF_114) Early life insults to the developing lung include intrauterine growth restriction, prenatal and postnatal exposure to tobacco smoke and other pollutants, and preterm delivery. These insults are associated with increased rates of asthma in childhood, risk of childhood respiratory disease, and in genetically susceptible individuals, COPD.[115-117](#_ENREF_115) As noted, obstructive lung diseases are notably increased in HIV-infected individuals.[62](#_ENREF_62) It appears that HIV compounds the detrimental effect of smoking, and may similarly accelerate disease in those exposed to other risk factors, including bacterial infections and TB.

Nutritional deficiencies (malnutrition and micronutrient) are associated with significant morbidity and mortality in childhood.[118](#_ENREF_118) These are more common in HIV-infected individuals, and in LMIC. In zinc deficient areas, supplementation is safe and can reduce infection rates in children.[119](#_ENREF_119),[120](#_ENREF_120) Wider nutritional deficits account for geographical differences in respiratory infection in children, and may be improved by targeted interventions.[118](#_ENREF_118)

## Environmental factors

Global risk factors for respiratory ill-health include air pollution, occupational exposure to particulates, asthmagens, heavy metals, carcinogenic hydrocarbons and inorganic dusts.[121](#_ENREF_121) Currently, there is insufficient evidence to comment on the potential additional effect of HIV in the particulate exposed lung, but global variability in these exposures is likely to explain some variation in HIV-associated lung disease. For example, household air pollution (HAP) is the third most important risk factor for disease worldwide, due to the enhanced risk of lower respiratory tract infection, but also COPD.[121](#_ENREF_121),[122](#_ENREF_122) By increasing the incidence of respiratory infection, HAP could promote recurrent infections and bronchiectasis. Similarly, epidemiological associations between HAP and tuberculosis are difficult to disentangle due to co-location, but household air pollution might also be expected to increase TB transmission in LMIC with high HIV prevalence. [123](#_ENREF_123),[124](#_ENREF_124)

## Health systems and the wider context

Many countries that have experienced a heavy burden of HIV had pre-existing weak health systems that were overwhelmed by the advent of the HIV epidemic. A public health approach to treatment, with simplified treatment protocols, task-shifting and minimal monitoring, has made it possible to treat large numbers of HIV-infected people.[125](#_ENREF_125) The consequence of this remarkable success is an increasing incidence of chronic complications as people live longer. In many high HIV prevalence settings, health systems, already overwhelmed by the burden of providing chronic HIV care, lack of the capacity to diagnose and manage chronic disease.[62](#_ENREF_62)[126](#_ENREF_126) However, integrating services for HIV and non-communicable diseases has the potential to leverage the success of ART rollout in providing care for other chronic diseases.[127](#_ENREF_127)

The poorest urban populations in LMIC are exposed to higher levels of communicable diseases, pollution, malnutrition, and may be poorly served by healthcare services.[128](#_ENREF_128) Rapid, unplanned development increases urban disparities in health outcomes. For example, HIV increases the risk of tuberculosis, and overcrowding and poor housing promote transmission of tuberculosis.[129](#_ENREF_129),[130](#_ENREF_130) All of these factors may influence the degree to which HIV-infected individuals in LMIC are faced with co-morbid challenges to their health, particularly infection.[131](#_ENREF_131) In many low income settings, the lack of diagnostic capacity means there is a paucity of evidence about relative burdens of disease, and less well refined local clinical management guidelines. In addition, weak health systems may be further compromised by external factors such as natural disasters, political and economic instability.

Data from high-income settings countries has demonstrated a tripling of mortality rates in HIV-infected individuals who smoke compared with the background population.[132](#_ENREF_132),[133](#_ENREF_133) Rising tobacco use, and relatively weak tobacco control frameworks in LMIC, are projected to cause an increase in chronic respiratory disease and malignancy.[134](#_ENREF_134) The risk may be even higher among those living with HIV.

# Prevention of HIV-related respiratory illness

## Co-trimoxazole

Co-trimoxazole is effective against several respiratory pathogens including *P. jirovecii*, and bacteria such as *S. pneumoniae*, *H. influenza,* and *S. aureus* and antibiotic prophylaxis with co-trimoxazole in HIV-infected individuals reduces mortality in adults and children independent of ART.[135-137](#_ENREF_135) Recommendation of co-trimoxazole prophylaxis has resulted in lower rates of PCP and bacterial pneumonia, even where antibiotic resistance rates are high.[138-140](#_ENREF_138) Recent review of available data, and subsequent recommendations from the WHO, suggest that in resource-rich settings co-trimoxazole prophylaxis can be stopped after immune reconstitution induced by ART.[141](#_ENREF_141),[142](#_ENREF_142) However, in sub-Saharan Africa, continued co-trimoxazole prophylaxis is associated with a mortality benefit even after immune reconstitution.[143](#_ENREF_143) This is thought to be due to its broader effects on malaria prophylaxis and prevention of severe bacterial infections, rather than prevention of PCP, which is uncommon at higher CD4 counts.[144](#_ENREF_144) In the recent past, rates of co-trimoxazole uptake, especially in sub-Saharan Africa, have been sub-optimal due to weak drug supply chains despite relatively low drug costs.[145](#_ENREF_145),[146](#_ENREF_146) Individual factors for non-use include a lack of understanding of therapies by caregivers and healthcare workers, highlighting the importance of patient education.[147](#_ENREF_147)

## Isoniazid prophylaxis therapy (IPT)

Given the high risk of TB in HIV-infected individuals, the WHO recommends systematic screening for TB, with use of isoniazid prophylaxis therapy (IPT) after exclusion of active disease as an essential component of the HIV care package.[148](#_ENREF_148),[149](#_ENREF_149) While IPT reduces tuberculosis incidence, scale-up of IPT has been slow, with only 14 of 41 high TB/HIV burden countries reporting having implemented IPT in 2013.[107](#_ENREF_107),[149](#_ENREF_149),[150](#_ENREF_150) Challenges to implementation include difficulties in identifying latent disease and excluding active disease, health-system barriers including lack of integration of HIV and TB services, weak supply chain management, and ongoing uncertainty regarding the duration of treatment and length of protection provided by IPT.[145](#_ENREF_145),[151](#_ENREF_151)

## Immunization

In the general population immunization is effective in reducing disease from *S. pneumoniae*, *H. influenzae* type b (Hib), influenza, measles and pertussis. HIV-infected persons may have a diminished antibody response to pneumococcal vaccine with protection inversely correlated with the degree of immunodeficiency.[152-157](#_ENREF_152) Responses are often lower in HIV-infected patients with CD4 counts <500 cells/mL than in those with higher CD4 cell counts[156](#_ENREF_156). HAART is expected to improve the efficacy of vaccination, but humoral responses may remain sub-optimal, even after pneumococcal revaccination[158](#_ENREF_158),[159](#_ENREF_159) However, pneumococcal immunisation with protein conjugate vaccine (PCV) in HIV-infected infants reduces invasive disease and pneumonia incidence, and is recommended.[160](#_ENREF_160) Pneumococcal immunisation in HIV-infected adults in LMIC is less well studied, and has mixed results in resource-limited settings: an early Ugandan RCT of polysaccharide vaccination (PPV) suggested potential harm.[161](#_ENREF_161) However, more recently conjugate vaccination as secondary pneumococcal prevention in Malawi has been shown to give limited protection against invasive disease, but not pneumonia.[162](#_ENREF_162) A prime-boost approach, using PCV initially followed by PPV-23 boosting, appears to improve responses in both children and adults but has not undergone clinical trials.[163](#_ENREF_163).

Hib conjugate vaccines are immunogenic in HIV infected children and adults,[164](#_ENREF_164),[165](#_ENREF_165) although antibody levels are reduced compared with HIV uninfected controls, and appear to be proportional to CD4 count.[166](#_ENREF_166),[167](#_ENREF_167) Preliminary studies of the trivalent inactivated influenza vaccine in HIV-infected adults suggest a decreased incidence of laboratory-confirmed disease, but limited data on other outcomes, and no effect on risk of pneumonia, hospitalization rates, or mortality has been shown.[168](#_ENREF_168)

In addition to issues of efficacy, there are large global variations in availability and uptake of these vaccines.[169](#_ENREF_169) For example, influenza vaccination is rarely available in LMIC. Vaccine effectiveness will depend on maintaining appropriate storage conditions such as the “cold chain”. The WHO Effective Vaccine Management project gauges the vaccine programme quality of 65 LMIC using multiple criteria: currently, 26% achieve the minimum standard of temperature control and only 20% have adequate systems and procedures for stock management.[170](#_ENREF_170) Expansion of vaccine availability and use is being driven by the Global Alliance for Vaccines and Immunization (GAVI) programme, but in 2014 there was still a significant gap between protocol and delivery, and the third dose of pneumococcal vaccine was only delivered in 28% of GAVI-eligible countries.[171](#_ENREF_171)

## Measures to reduce nosocomial transmission

Inadequate infection control in health facilities is a global problem.[172](#_ENREF_172) Nosocomial spread of TB is of particular concern in areas of high HIV prevalence. A widely publicised outbreak of XDR-TB in Tugela Ferry, South Africa (an area of very high HIV prevalence) had a 98% mortality. Modelling this epidemic suggests that 9/10 XDR-TB transmission occur in hospitals.[173](#_ENREF_173) Implementation of transmission reduction measures is limited by resources.[174](#_ENREF_174),[175](#_ENREF_175) However, the same model predicts that by using combination interventions (ventilation, isolation, early hospital discharge, respiratory mask use and ART provision), case transmission could fall by almost half.[173](#_ENREF_173)

# Assessment of HIV-related respiratory disease

## Investigation of infection

Investigation of infectious disease in HIV-infected individuals must take account of “conventional” pathogens, and of additional opportunistic infections. Further, multiple co-existing pathology is common: a Spanish study of HIV-infected individuals receiving ART and presenting with features of pneumonia showed that 9% had at least two aetiological agents identified.[176](#_ENREF_176) In resource-limited settings, identification of any pathogen may be difficult. Microbial identification is frequently limited to Gram and ZN staining in many secondary-level healthcare facilities. Bacterial culture is frequently not available, and examination for fungi, which requires additional staining and culture, is not routinely available. Imaging investigations may also be limited to plain film radiology, e.g. CXR, which provides limited discriminatory information when compared to thoracic CT. Bronchoscopy and lavage, despite its documented utility in numerous studies from high-income countries, is rarely available in LMIC, even in secondary and tertiary level settings. All of these factors may impact on delay in diagnosis, resulting in lower rates of treatment success.

Bias in the availability of tests may lead to the systematically under-diagnosis of some illnesses, although data are difficult to interpret. For example, in early series of HIV-infected adults, PCP was considered to be uncommon as an AIDS-defining illness in Africa compared with the USA.[177](#_ENREF_177) It has been suggested that this phenomenon may represent a masking of the relatively non-pathogenic *P. jirovecii* by other infectious disease in LMIC, although diagnostic bias may play a part.[52](#_ENREF_52) Other fungal infection in LMIC (e.g. *H. capsulatum* and *Coccidiodes immitis)* are equally poorly defined, and likely to be misdiagnosed as community-acquired pneumonia*.*[178](#_ENREF_178)

Rapid diagnosis of disseminated cryptococcal disease has been improved by antigen testing (CrAg) in serum or cerebrospinal fluid. While serum CrAg is sensitive as a screening method, it is not specific for lung disease, and antigen testing on BAL fluid does not infer that *Cryptococcus* is the primary pathology.[54](#_ENREF_54),[179](#_ENREF_179),[180](#_ENREF_180)

The capacity and direction of TB diagnostics in areas of high HIV prevalence has been reviewed elsewhere.[181](#_ENREF_181),[182](#_ENREF_182) Sputum smear microscopy is the mainstay of diagnosis, although recent roll-out of Xpert MTB/RIF is likely to aid early identification of mycobacterial infection, but may not necessarily improve outcomes without strengthening of health systems.[183](#_ENREF_183),[184](#_ENREF_184)

## Investigation of non-infectious causes of lung disease

Non-infective causes of lung disease in HIV are rarely diagnosable on clinical history alone. While airway obstruction is prevalent in HIV cohorts from the US, obstructive lung disease is less well recognised in LMIC due to the widespread lack of spirometry.[61](#_ENREF_61),[185](#_ENREF_185)[62](#_ENREF_62),[185](#_ENREF_185) Performing assessment to American Thoracic Society standards in resource-limited settings has proved to be challenging.[186](#_ENREF_186)

Post-infective lung disease is an important cause of chronic respiratory symptoms. Bronchiectasis may be caused by recurrent respiratory tract infections and tuberculosis. While florid cases might be identifiable clinically, those with earlier stage disease, require CT scanning for a definitive diagnosis.[73](#_ENREF_73)[7](#_ENREF_7),[187](#_ENREF_187),[188](#_ENREF_188)[7](#_ENREF_7),[187](#_ENREF_187),[188](#_ENREF_188) Similarly, there is a high prevalence of chronic respiratory symptoms in older children and adolescents, which is frequently managed as tuberculosis. Obliterative bronchiolitis (OB) has recently been described as the most common cause of chronic lung disease in this age-group. This condition is difficult to diagnose without CT, unlike LIP which is usually apparent on plain radiography, and may explain why OB is not usually identified in children.[84](#_ENREF_84) Interstitial lung disease may be apparent on CXR in advanced cases, but without chest CT and more complex measures of lung physiology, such as lung volumes (to confirm restrictive lung defects), and transfer factor (to aid in severity assessment), diagnosis of interstitial lung disease is extremely challenging.[60](#_ENREF_60),[82](#_ENREF_82)

Lastly, given that the differential diagnosis of chronic respiratory symptoms in HIV-infected individuals, (e.g. cough and exertional dyspnoea) includes cardiac disease, it is of concern that echocardiography is limited in most LMIC to tertiary centres.

## Diagnostic algorithms

Given the lack of diagnostic tools, chronic symptoms are often not investigated and individuals are treated empirically for TB in the context of HIV. Clinical algorithms may provide a systematic approach to investigating chronic respiratory symptoms.

Algorithms for investigation and management of chronic respiratory symptoms in HIV-infected individuals in LMIC have been used in primary, secondary, and tertiary care settings. Different systems have been developed by WHO (1991), Medicines sans Frontiers (MSF, 2001), and the University Hospital of Kigale, Rwanda (CHUK).[189-191](#_ENREF_189) The WHO and MSF algorithms were developed before widespread ART availabilty, and the CHUK algorithm is derived from a relatively small dataset from a single centre. None of the algorithms consider cardiac disease as a major differential in their pathway. Recently these three algorithms were virtually compared in a cohort of hospitalised HIV-infected patients with chronic cough.[191](#_ENREF_191) The main diagnoses were TB and PCP, but other diagnoses including lobar pneumonia, empyema, and pulmonary Kaposi sarcoma were also included. The diagnostic sensitivity of the algorithms was 70%, 88% and 95.7% for the WHO, MSF and CHUK algorithms respectively. Mean time to appropriate management was 3.46 days (MSF) and 1.86 days (CHUK). “Harm”, being the result of false positive and false negative diagnoses, was highest for the WHO algorithm. The CHUK algorithm was the most complex, and while it was associated with higher sensitivity and less harm, the resulting complexity may limit its utility in many LMIC settings.

An example of a practical algorithm for use in primary and secondary level settings in LMIC is shown in Figure 2. This is based on utilising available/feasible investigations, and focuses on those that are most likely to influence local clinical management. Evidence to support trials of “empiric” treatment interventions as diagnostic tools in both resource-rich, and resource-poor settings is lacking, but may be helpful in certain circumstances. For example, while spirometry is insensitive in diagnosing asthma, reversible obstruction is highly specific where is occurs.[192](#_ENREF_192) Longer trials of inhaled corticosteroids (1 month or more) are needed to evaluate improvement in peak flow or symptom control, but are frequently not possible due to lack of availability.[193](#_ENREF_193) If congestive cardiac failure is considered, symptomatic response to diuretics might clarify the diagnosis.[193](#_ENREF_193)

# Management of HIV-associated lung disease

Globally, antibiotics are widely available, and in LMIC, they frequently form the basis of initial trials of empiric treatment where diagnostic services are lacking. Internationally recognised systems support this approach to management e.g. the WHO Integrated Management of Childhood Illness (IMCI), and the Integrated Management of Adolescent and Adult Illness (IMAI).[194](#_ENREF_194),[195](#_ENREF_195) In order to safely identify all treatable infection in primary level facilities, broad definitions of respiratory infection are used. For example, using IMAI, both “cough with tachypnoea” and “difficulty breathing with chest pain” in the absence of markers of severe disease should be prescribed an antibiotic. While these clinical approaches are understandable given the lack of laboratory facilities, the implication is that the most prevalent diagnoses are over-treated, and that less common pathology (especially chronic disease) is untreated and unrecognised. Recurrent use of antibiotics within such clinical pathways is likely. Presumptive treatment may therefore drive the increasing rates of antibiotic resistance in LMIC, in combination with inappropriate use of antibiotics by physicians and unskilled practitioners, and by the public who may purchase “over the counter” medication. [196](#_ENREF_196),[197](#_ENREF_197) The broader LMIC health environment therefore facilitates both the evolution of resistant pathogens and their rapid spread in the community.[198](#_ENREF_198)

## Availability of drugs and monitoring

Drug availability in LMIC is often defined by the WHO “Essential Medicines” List,[199](#_ENREF_199) which includes a variety of antimicrobial agents appropriate to first-line treatment of infection. In resource-rich systems, with low burdens of infectious diseases, resistance to first-line antibiotics can be overcome by use of second-line and third-line agents. In LMIC, where pathogen resistance emerges, medications are frequently expensive or unavailable, for example, carbapenems.

Similarly, TB treatment programmes are designed to ensure access to drug-sensitive disease. Services for MDR and XDR-TB are improving. However, significant limitations to expansion currently exist: a lack of widespread expertise; expensive drugs; the need for robust pharmacovigilance systems, especially with concurrent ART.[37](#_ENREF_37)

Systemic antifungals, except fluconazole, have limited availability in LMIC, which limits treatment possibilities for endemic fungal pneumonia to this less effective fungistatic agent.[200](#_ENREF_200) Similarly, cryptococcal disease is also frequently treated with fluconazole despite clear evidence of more effective flucytosine and amphotericin B.[201](#_ENREF_201),[202](#_ENREF_202) Despite being added to the Essential Medicines list, national drug licensing issues and production costs may impede their use.[195](#_ENREF_195)

Similar issues affect the treatment of obstructive lung disease and malignancy. Drugs on the WHO “Essential Medicines” list, including bronchodilators and inhaled corticosteroids, are underused in in LMIC, by comparison with resource-rich countries. In large part this is due to cost to the user, both in terms of purchase cost of medication and the indirect opportunity costs, such as travel and loss of income from attending healthcare facilities.[203](#_ENREF_203) Long-term antibiotics for chronic lung disease are in limited supply, as well as access to non-pharmacological management such as physiotherapy.[204](#_ENREF_204)

Critical care has been consistently overlooked as a specialty in LMIC, likely due to high per-patient costs. Equipment and human resources are lacking and triage systems which underlie critical care services are frequently weak.[205](#_ENREF_205) While nihilistic attitudes to the critically-unwell patient may frequently be justified, simple measures can improve quality of care and outcome measures.[205](#_ENREF_205) One obvious example is supplemental oxygen availability, which even in tertiary-care settings is limited; provision of domiciliary oxygen treatment is non-existent.[206](#_ENREF_206),[207](#_ENREF_207) Treatment of respiratory failure is often limited to low flow oxygen concentrators, with little capacity for assisted ventilation.[208](#_ENREF_208) Healthcare providers may be insufficiently trained to support the safe delivery of critical care, where a lack of infrastructure, clinical knowledge and training seems to be more significantly limiting than the availability of drugs.[209](#_ENREF_209),[210](#_ENREF_210)

# Future direction

Continued focus on improving ART capacity, and integrating care with that of concurrent chronic disease is likely to result in significant improvements in lung health for HIV-infected individuals. Earlier diagnosis and treatment of HIV should reduce the incidence of structural lung disease from recurrent infections. However, increased longevity may unmask disease related to chronic inflammation in the lung. The pathology of chronic lung disease is unclear, especially our understanding of the interaction between immune dysregulation and the lung microbiome. Although the Lung HIV Microbiome Project has recently found few significant differences between US based HIV-infected and non-infected individuals, the generalisability to LMIC is unknown.[211](#_ENREF_211) Clinical trials of therapy to reduce inflammation and ongoing low-level infection are underway (e.g. azithromycin therapy for HIV-related chronic lung disease).[212](#_ENREF_212) However, biochemical and pharmacological research should occur in parallel with preventative strategies of known importance: strong tobacco control is urgently needed. While tuberculosis case fatality rates are falling, the challenges of MDR and XDR-TB require robust diagnostic and public health systems for identifying at risk individuals. Provision of antimicrobials in the context of resistant TB and other infections should be improved in conjunction with systems for antimicrobial stewardship.

There is a pressing need to develop systems relevant to the resources available in LMIC, particularly to move the investigation and management of chronic respiratory pathology beyond tuberculosis. This will require deeper investigation of the pathogenesis of such illnesses. However, pragmatic clinical research will be paramount: developing, validating and integrating diagnostic and treatment pathways could rapidly improve efficiency and effectiveness within health systems. These should be targeted at low cost and targeted interventions which could be incorporated into routine care without the need for secondary or tertiary level investigation where possible. Syndromic management, spirometry, and “one off” enhanced diagnostic imaging should be evaluated for their potential to improve long term lung health. Finally, as healthcare systems develop, critical care facilities will become more important in providing acute, targeted support of respiratory care. In this context, large improvements could be made in a relatively small number of individuals, although key questions include how we should maximise the cost-effectiveness of such facilities.

It is clear that HIV-related respiratory disease is significantly different in LMIC, due to the epidemiology of pathogens, weaker healthcare delivery systems, and broader economic limitations. As the burden of chronic disease in the general population increases, HIV-related lung disease is likely to mirror this pattern. A combination of laboratory research, clinical investigation and health systems strengthening has exciting potential for improving the health of some of the most disadvantaged.

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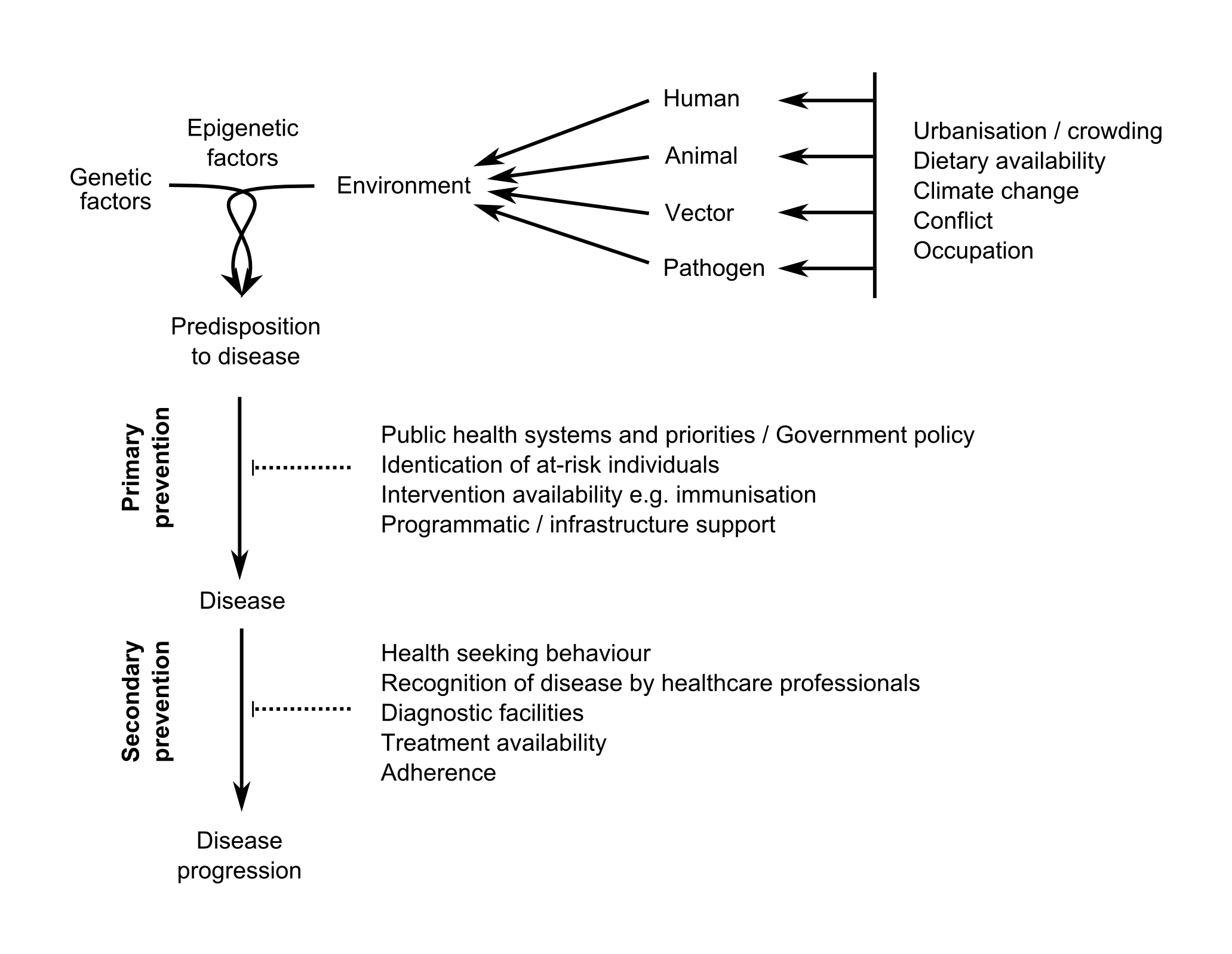
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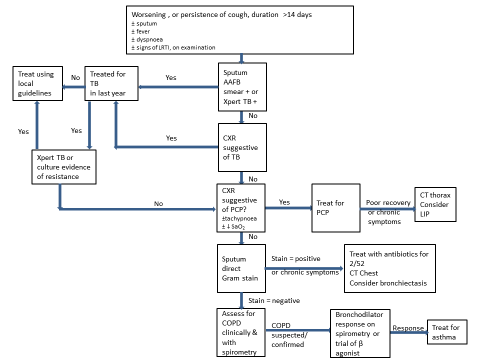
# Figure 1

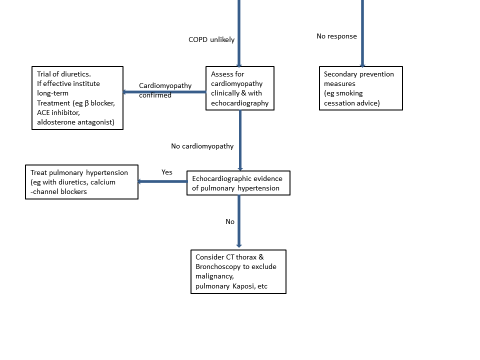
An outline of factors which impact on the global variations in the epidemiology of HIV related lung disease, particularly those which act disproportionately in low and middle income countries



# Figure 2

Investigating chronic cough and breathlessness in HIV-infected adults: a suggested algorithm.





**Key**: AAFB = acid- and alcohol-fast bacilli, CXR = chest radiograph, PCP = *Pneumocystis jirovecii* pneumonia, SaO2 = transcutaneous oxygen saturations, LIP = lymphocytic interstitial pneumonia, CT = computer tomography, COPD = chronic obstructive pulmonary disease, ACE = angiotensin converting enzyme