

AAT Protein's Role in Lung Health Beyond COPD & Severe Asthma

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While alpha-1 antitrypsin deficiency (AATD) is a recognised genetic cause of emphysema and liver disease, the broader implications of AAT protein levels for general lung health, independent of severe deficiency, warrant further consideration. Data presented at ATS 2026 underscored that AAT's protective functions extend beyond the established AATD context, suggesting its relevance in a wider spectrum of pulmonary conditions.

KEY TAKEAWAYS

- The Pivot: AAT protein's role in lung health is not confined to severe genetic deficiency but impacts general pulmonary integrity.
- The Data: Normal-range AAT levels correlate with reduced inflammatory markers and improved lung function parameters in non-AATD populations.
- The Action: Clinicians should consider AAT's broader anti-inflammatory and tissue-protective mechanisms when evaluating chronic lung conditions, even in the absence of classic AATD.

Alpha-1 antitrypsin (AAT) is a serine protease inhibitor primarily synthesised in the liver, with its main physiological role being the inhibition of neutrophil elastase (NE) in the lungs.¹ Uncontrolled NE activity contributes to the degradation of elastin and other extracellular matrix components, a process central to the pathogenesis of emphysema.² While severe genetic deficiency of AAT (AATD) is a well-established risk factor for early-onset emphysema and liver disease, the focus at ATS 2026 expanded to the role of AAT protein within the normal range and its influence on lung health in populations without classic AATD.³ This perspective highlights AAT not merely as a deficiency marker but as a critical component of the lung's innate defence against proteolytic damage and inflammation.

AAT's Broader Protective Mechanisms

Beyond its primary role as an NE inhibitor, AAT exhibits pleiotropic effects, including anti-inflammatory, immunomodulatory, and anti-apoptotic properties.⁴ These functions are relevant in various inflammatory lung diseases, not exclusively AATD-related conditions. For instance, AAT has been shown to modulate cytokine production, inhibit NF- κ B activation, and protect epithelial cells from oxidative stress and apoptosis.⁵ These mechanisms suggest that even subtle variations in AAT levels within the normal range, or alterations in its functional activity, could influence susceptibility to, or progression of, chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and severe asthma, where inflammation and tissue remodelling are prominent features.⁶

Presentations at ATS 2026 detailed studies exploring the correlation between AAT levels and lung function parameters, as well as inflammatory biomarkers, in cohorts of individuals without diagnosed AATD. One observational study, for

example, examined a cohort of N=850 individuals with mild-to-moderate COPD and found that those in the highest quartile of serum AAT levels (mean 1.5 g/L) exhibited a slower annual decline in forced expiratory volume in 1 second (FEV1) compared to those in the lowest quartile (mean 0.9 g/L).⁷ The difference in FEV1 decline was -15 mL/year (95% CI: -28 to -2 mL/year, P=.03), suggesting a protective effect even within the normal physiological range.⁷ Further data highlighted AAT's role in mitigating airway inflammation. In a separate analysis of N=320 patients with severe asthma, individuals with higher baseline AAT levels demonstrated reduced sputum neutrophil counts (mean reduction of 2.3%, 95% CI: 1.1% to 3.5%, P=.001) and lower levels of interleukin-8 (IL-8) in bronchoalveolar lavage fluid (BALF) (mean reduction of 18 pg/mL, 95% CI: 10 to 26 pg/mL, P) following a standard course of inhaled corticosteroids.⁸ These findings imply that AAT may enhance the anti-inflammatory response to conventional therapies or directly contribute to a less inflammatory airway milieu.⁸

The implications extend to conditions beyond COPD and severe asthma. The anti-apoptotic effects of AAT, for instance, could be relevant in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), where alveolar epithelial cell death is a critical pathological event.⁹ Preclinical models have demonstrated that exogenous AAT administration can reduce lung injury and improve survival in experimental models of ALI by preserving epithelial integrity and reducing inflammatory cell infiltration.¹⁰ While these are preclinical observations, they underscore the broad therapeutic potential of AAT as an anti-inflammatory and tissue-protective agent.

Limitations and Future Directions

The presented data, while compelling, largely stem from observational studies and preclinical models. The precise mechanisms by which normal-range AAT levels exert their protective effects in diverse lung conditions require further elucidation. Confounding factors, such as genetic polymorphisms influencing AAT function rather than just concentration, or interactions with other protease-antiprotease systems, were not fully addressed in all presentations.¹¹ Future research needs to focus on prospective interventional studies to determine if modulating AAT levels or enhancing its functional activity can translate into tangible clinical benefits for patients with chronic inflammatory lung diseases who do not have AATD. The development of novel AAT-based therapies or strategies to boost endogenous AAT production could represent a new avenue for therapeutic intervention in a broader range of pulmonary disorders.¹²

CLINICAL IMPLICATIONS

The discussions at ATS 2026 regarding alpha-1 antitrypsin (AAT) protein suggest a necessary recalibration of our understanding. For too long, AAT has been largely confined to the niche of severe genetic deficiency, primarily impacting a relatively small patient population. The emerging evidence, however, points to AAT as a fundamental component of lung homeostasis, influencing inflammation and tissue integrity across a wider spectrum of pulmonary conditions. This implies that clinicians should begin to view AAT not merely as a diagnostic marker for a rare disease, but as a potential therapeutic target or even a prognostic indicator in more common conditions like COPD and severe asthma.

This expanded perspective could prompt a re-evaluation of current treatment paradigms. If AAT's anti-inflammatory and tissue-protective effects are indeed significant even at normal physiological concentrations, then strategies to optimise endogenous AAT activity, or even consider augmentation therapy in select non-AATD patients, might become relevant. While current guidelines from bodies like the American

Thoracic Society (ATS) and European Respiratory Society (ERS) restrict augmentation therapy to those with severe AATD, the data presented could lay the groundwork for future trials exploring AAT in patients with rapidly progressive COPD or refractory severe asthma, irrespective of their AAT genotype. This would represent a significant shift for manufacturers of AAT augmentation therapies, potentially broadening their market beyond the current orphan drug designation.

For patients, this could mean a more nuanced approach to managing chronic lung disease. Instead of focusing solely on bronchodilators and corticosteroids, future therapeutic strategies might incorporate interventions aimed at bolstering the lung's intrinsic protective mechanisms, of which AAT appears to be a key player. While it is premature to recommend widespread AAT testing or augmentation in non-AATD patients, the scientific community is clearly moving towards a more holistic understanding of lung resilience. This intellectual pivot, if supported by robust interventional data, could ultimately lead to more personalised and effective treatments for a larger population suffering from debilitating lung conditions.

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