

AATD: Aiming for AAT Restoration and Clinically Meaningful Endpoints

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Alpha-1 Antitrypsin Deficiency (AATD) is an inherited disorder characterised by low circulating levels of alpha-1 antitrypsin (AAT), primarily leading to early-onset emphysema and liver disease. Current augmentation therapy aims to increase plasma AAT levels, but the direct impact on clinically meaningful outcomes remains an area of ongoing investigation. The focus at ATS 2026 will be on novel therapeutic strategies designed to restore AAT levels more effectively and to demonstrate tangible clinical benefits beyond biochemical markers.

KEY TAKEAWAYS

- ° The Pivot: New therapeutic approaches for AATD are moving beyond plasma AAT level augmentation to direct AAT restoration and clinically meaningful endpoint assessment.
- ° The Data: Future trials are expected to report on endpoints such as lung function decline (e.g., FEV1), exacerbation rates, and quality of life measures, rather than solely AAT plasma concentrations.
- ° The Action: Clinicians should anticipate a shift in AATD management, with potential for therapies that offer more targeted AAT restoration and demonstrable improvements in patient outcomes.

Alpha-1 Antitrypsin Deficiency (AATD) results from mutations in the SERPINA1 gene, leading to misfolded AAT protein that accumulates in hepatocytes and is deficient in the circulation.¹ This deficiency predisposes individuals to neutrophil elastase-mediated lung destruction, manifesting as emphysema, and can cause liver cirrhosis due to protein aggregation.² Current standard of care for lung disease involves weekly intravenous augmentation therapy with purified human plasma-derived AAT.³ While this therapy increases plasma AAT levels, its efficacy in slowing lung function decline has been debated, with some studies showing modest benefits in FEV1 decline over several years.⁴ The challenge lies in demonstrating a direct, statistically significant impact on hard clinical endpoints, such as hospitalisations for respiratory exacerbations or mortality, in adequately powered trials.⁵

The ATS 2026 conference is expected to highlight advancements in AATD research, particularly focusing on strategies that aim for more complete AAT restoration and the evaluation of clinically meaningful endpoints. These advancements include gene therapies, RNA interference (RNAi) therapeutics, and small molecule chaperones. Gene therapy approaches, for instance, aim to introduce a functional copy of the SERPINA1 gene into hepatocytes, enabling endogenous production of AAT.⁶ Early-phase trials in this area have focused on safety and preliminary evidence of AAT expression.⁷ RNAi therapeutics, conversely, target the reduction of mutant Z-AAT protein production in the liver, thereby mitigating liver disease and potentially freeing up cellular machinery to produce more functional AAT if combined with augmentation or gene therapy.⁸ Small molecule chaperones are designed to assist the proper folding and secretion of mutant AAT, increasing circulating levels.⁹

Advancements in Therapeutic Strategies and Endpoints

The shift in therapeutic development for AATD is towards achieving AAT restoration, which implies not just increasing circulating levels but also ensuring the protein is functional and correctly distributed. This contrasts with augmentation therapy, which primarily supplements AAT. Future trials are expected to incorporate more rigorous clinical endpoints. Beyond the traditional FEV1 decline, which has been a primary endpoint in many AATD trials, researchers are increasingly considering other measures. These include quantitative computed tomography (CT) densitometry to assess lung parenchymal destruction, which provides a more direct measure of emphysema progression.¹⁰ Respiratory exacerbation rates, a significant driver of morbidity and healthcare utilisation in AATD patients, are also gaining prominence as a primary or key secondary endpoint.¹¹

Patient-reported outcomes (PROs) and quality of life (QoL) measures are also becoming integral to trial design. Tools such as the St. George's Respiratory Questionnaire (SGRQ) or the AATD-specific QoL questionnaire can capture the patient's perspective on symptom burden and functional status.¹² For liver disease, endpoints include liver stiffness measured by transient elastography, serum transaminase levels, and liver biopsy for fibrosis assessment.¹³ The goal is to move beyond surrogate biochemical markers to demonstrate a tangible benefit that resonates with both clinicians and patients. For example, a reduction in the annual rate of FEV1 decline by 20-30 mL/year, a decrease in severe exacerbations by 25%, or an improvement in SGRQ total score by 4 units are considered clinically meaningful thresholds in chronic obstructive pulmonary disease (COPD) and AATD.¹⁴

Limitations in AATD research often include the relatively small patient population, which can make large-scale, long-term trials challenging to power adequately for rare disease endpoints.¹⁵ The heterogeneity of disease progression among individuals with AATD also complicates trial design and interpretation.¹⁶ Future directions involve biomarker identification to stratify patients who are most likely to benefit from specific therapies and the development of

combination therapies that address both lung and liver manifestations. The integration of real-world evidence and advanced analytical techniques, such as artificial intelligence for image analysis, may also help to overcome some of these limitations and accelerate the development of effective AATD treatments.¹⁷

CLINICAL IMPLICATIONS

The shift in AATD research towards direct AAT restoration and clinically meaningful endpoints signals a maturation of the field. For clinicians, this means a potential move away from therapies that merely augment plasma levels to those that offer a more fundamental correction of the underlying defect. While augmentation therapy has been the cornerstone for decades, its impact on hard clinical outcomes has been modest, leaving a significant unmet need. The prospect of gene therapies or RNAi therapeutics, if proven safe and effective, could fundamentally alter the management paradigm, potentially offering a one-time or infrequent treatment that prevents disease progression rather than merely slowing it.

The industry's focus on endpoints like lung CT densitometry, exacerbation rates, and patient-reported outcomes is a welcome development. It reflects an understanding that a drug's value is not solely in its ability to normalise a lab value, but in its capacity to improve a patient's life. This emphasis will likely drive more rigorous trial designs and potentially lead to therapies that offer a more compelling value proposition to healthcare systems. However, the cost-effectiveness of these advanced therapies, particularly gene therapies, will be a critical consideration for payers and healthcare providers, necessitating robust long-term efficacy and safety data.

For patients, these advancements offer hope for more effective treatments that could halt or even reverse disease progression, rather than just mitigating symptoms. A therapy that reduces exacerbations or improves quality of life by a clinically meaningful margin would be transformative. However, the journey from promising research to approved therapy is long, and patients should be aware that these novel approaches are still largely in early development. Continued advocacy for research funding and participation in clinical trials will remain essential to bring these potential breakthroughs to fruition.

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