Belgian Guidelines for Diagnosis and Management of Patients with α1-Antitrypsin Deficiency

Belgian Thoracic Society’s α1-Antitrypsin Deficiency Working Party


1. Summary and practical considerations

1.1. Screening for α1-Antitrypsin (AAT) deficiency should be systematically performed on patients with emphysema (regardless of smoking history), COPD, bronchiectasis without evident aetiology, asthma with persistent obstruction despite treatment, liver disease without evident aetiology, offspring or parents of an individual with an AAT deficiency (first degree collaterals), absence of an AAT peak on electrophoresis, and unexplained panniculitis or anti-proteinase-3 vasculitis.

1.2. The result of a normal or abnormal AAT serum level should be saved in the appropriate section of the patient’s record to avoid needless retesting.

1.3. Patients with an AAT serum level < 114 mg/dL should undergo a pheno- and/or genotyping by sending appropriate samples to one of the reference labs in Belgium or by sampling three large blood droplets (0,5 mL of blood in total) on a special card (dried blot spots).

1.4. Cards can be obtained at no cost from the secretariat of the Belgian Society of Pneumology: Agnes Tommeleyn; email address: info@bvp-sbp.org

1.5. Cards should be sent by post to the BVP/SBP secretariat, Eendrachtstraat 56/Rue de la Concorde 56 1050 Brussels after filling in clinical and administrative data. She will forward it to the European reference laboratory (Warburg, Germany) for pheno- and genotyping. No costs will be charged, neither to the patient nor to the RIZIV/INAMI.

1.6. The Warburg Laboratory will communicate the result within 4 weeks to the physician.

1.7. In return, physicians are requested to register their patients with severe AAT deficiency (serum level < 50 mg/dL, PI*Null-Null, PI*Z-Null, PI* ZZ, PI*SZ, PI*S-Null), once the phenotype is known, either via the web site (http://www.air-registry.org/be/) or by regular mail. Physicians can obtain access to the Belgian Registry via info@bvp-sbp.org or sending a letter to the secretariat of the SBP-BVP.

1.8. Patients with severe AAT deficiency should be informed about the natural history of the disease and the importance of stopping smoking. Management of severe AAT deficiency should focus COPD treatment according to GOLD, aggressive treatment of pulmonary infections, vaccinations against influenza, hepatitis A and hepatitis B, annual follow-up of pulmonary function and imaging, liver tests, α-feto protein, liver echography. Augmentation therapy should be considered in non-or ex-smokers with AAT serum level under 50 mg/dL and with moderate to severe obstruction (FEV₁ between 30-65 % predicted) or with a rapid decline in FEV₁.
1.9. Genetic testing should be performed in all first degree collaterals of a homozygous or heterozygous α1-Antitrypsin deficient patient (Z or Null allele carrier). Genetic counselling could be provided.

2. **What is alpha-1 Antitrypsin [AAT] deficiency?**

AAT is a glycoprotein, synthesized essentially by the liver. AAT circulates in serum in concentrations of 150–300 mg/dL and inhibits neutrophil elastase, thus protecting the lung against unopposed proteases’ tissue destruction (tobacco smoking, infections…). AAT deficiency is a hereditary condition, characterized by a severe deficiency of this protein in serum and in tissues. Pulmonary emphysema of the panacinar type is the most prevalent clinical correlate of this deficiency and occurs because of an imbalance between the anti-elastase defenses of the lung and the relatively excessive action of leukocyte elastase.

Liver disease can also appear early in life (hepatitis) or, around 60 years old (cirrhosis, hepatocarcinoma), due to the toxic retention of a misfolded AAT in the liver.
3. Phenotypes and Genotypes

About 100 genetic variants of AAT have been identified to date.

The allele M is the normal variant of the protein. Two deficient alleles are regularly encountered in Belgium, Z (15 % of plasma normal values) and S (60 % of the normal values). Rare Null alleles exist with no secretion of AAT in the blood. The predominant normal phenotype is PI*MM, present in 94–96% of Caucasians. Approximately 2–3% of the Caucasian population is heterozygous (PI*MZ). Other important phenotypes are PI*MS, PI*MZ, PI*ZZ, PI*SZ, or PI*SS.

AAT deficiency occurs as the result of the inheritance of two protease inhibitor deficient alleles from the AAT gene, PI*Z being the most common (see Table 1). In the homozygous form (PI*ZZ), it results in low serum concentrations of AAT protein, usually below 50 mg/dL (less than 11 µmol/L) if measured by nephelometry.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>PM*MM</th>
<th>PM*MZ</th>
<th>PM*SS</th>
<th>PM*SZ</th>
<th>PM*ZZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>µM</td>
<td>20–48</td>
<td>17–33</td>
<td>15–33</td>
<td>8–16</td>
<td>2.5–7</td>
</tr>
<tr>
<td>mg/dL</td>
<td>150–350</td>
<td>90–210</td>
<td>100–200</td>
<td>75–120</td>
<td>20–45</td>
</tr>
</tbody>
</table>

Table 1. Range of serum levels of α₁-antitrypsin according to phenotype. Levels of less than 50 mg/dL (or 11 µmol/L) are associated with an increased risk for emphysema.

4. Quantative and qualitative tests

Serum AAT levels should be determined by nephelometry and expressed in mg/dL or in µmol/L (or µM). Inflammatory conditions may increase the steady state plasma AAT levels in Z heterozygous. A level of 11 µmol/L or 50 mg/dL is considered to be the “protective” threshold. Patients with severe AAT deficiency have plasma levels lower than 50 mg/dL.
Thin layer isoelectric focusing is the technique of choice used to identify AAT variants and is commonly referred to as “phenotyping”\textsuperscript{8}. It requires skill and experience and should be performed in reference laboratories. Isoelectric focusing can be performed on “dried blot spot” samples, using blood drops absorbed onto special blotting paper, allowing for easy transport.

Diagnosis at molecular level (“genotyping”) is performed on genomic DNA, extracted from circulating mononuclear blood cells. Lack of recognition of a known mutation may imply the presence of a new variant. Only genotyping permits us to detect patients with rare Null variants, in whom no AAT is produced.

5. Which features should prompt a suspicion of AAT deficiency?

Screening is indicated in the following situations, according to international ERS/ATS guidelines:

- Early-onset emphysema (at age of 45 years or less);
- Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.);
- Emphysema with prominent basilar hyperlucency;
- Unexplained liver disease;
- Necrotizing panniculitis;
- Anti-proteinase-3-positive vasculitis (C-ANCA) = Wegener vasculitis;
- Family history of any of the following: emphysema, bronchiectasis, liver disease, or panniculitis;
- Bronchiectasis without evident aetiology;
- Offspring or parents (first degree collaterals) of an individual with AAT deficiency.

The clinical settings in which quantitative testing is recommended are summarized in Table 2.

<table>
<thead>
<tr>
<th>No.</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Confirmation of absent α\textsubscript{1}-antitrypsin peak on serum protein electrophoresis</td>
</tr>
<tr>
<td>2</td>
<td>Early-onset pulmonary emphysema (regardless of smoking history)</td>
</tr>
<tr>
<td>3</td>
<td>Family members of known α\textsubscript{1}-antitrypsin–deficient patients</td>
</tr>
<tr>
<td>4</td>
<td>Dyspnea and cough occurring in multiple family members in same or different generations</td>
</tr>
<tr>
<td>5</td>
<td>Liver disease of unknown cause</td>
</tr>
<tr>
<td>6</td>
<td>All subjects with chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>7</td>
<td>Adults with bronchiectasis without evident aetiology should be considered for testing</td>
</tr>
<tr>
<td>8</td>
<td>Patients with asthma whose spirometry fails to return to normal with therapy</td>
</tr>
<tr>
<td>9</td>
<td>Unexplained panniculitis and anti–proteinase-3 vasculitis</td>
</tr>
</tbody>
</table>

*Table 2: Recommendations for quantitative testing of α\textsubscript{1}-antitrypsin deficiency (decreasing likelihood of finding a deficiency)*\textsuperscript{9}
6. Why screen for AAT deficiency?

Both the WHO and ATS/ERS guidelines recommend to screen patients’ categories, summarized in Table 2, to inform them as early as possible about the importance of an adapted lifestyle (avoidance of tobacco smoking\textsuperscript{10,11}, avoidance of environmental and professional pollutants and irritants), to establish as soon as possible preventive measures (vaccines, prompt treatment of respiratory infections, treatment of COPD and bronchial hyperresponsiveness, and the potential substitution treatment with AAT), to propose screening of collaterals, and to provide genetic prenatal advice.

7. Which patients should be phenotyped or genotyped?

Theoretically, all patients with a serum level of AAT below 150 mg/dL should be phenotyped. However, recent investigations by the AIR group indicate that only patients with an AAT level inferior to 114 mg/dL are carriers of Z or Null variants\textsuperscript{12,13}.

8. How to proceed with patients with AAT below 114 mg/dL?

Patients with serum level of AAT under 114 mg/dL should be phenotyped. Samples can be sent to the following laboratories in Belgium:

CHU Sart-Tilman, B-35 4000 Liège : Laboratoire de biochimie génétique

CHR de la Citadelle, Boulevard du Douzième-de-Ligne 1, 4000 Liège: Laboratoire médical
Alternatively, dried blood samples can be collected on a special card (dried blot spots), which should be sent to one European reference laboratory (Warburg, Germany), where a complete analysis will be done, including phenotyping and genotyping. Cards can be obtained, without cost, from the secretariat of the Belgian Society of Pneumology: Agnes Tommeley; email address: info@bvp-sbp.org

Approximately one half millilitre of blood is sufficient to fill 3 circles on the filter papers. After completion and drying, these cards should be returned to the secretary of the Belgian Society of Pneumology, who will send them to the reference laboratory, at no cost neither for the analysis nor for the shipping. Results may be expected within 3 weeks.
9. Why register patients in the Alpha1 International Registry (AIR)?

The Alpha1 International Registry (AIR) is a multinational research organization, founded in 1997 at the request of the WHO. It includes 21 countries including Belgium.

The main objectives of AIR are to establish an international database of patients, to promote basic and clinical research and to coordinate these activities. AIR collects, assesses and disseminates information concerning all aspects of AAT deficiency.

<table>
<thead>
<tr>
<th>Geographical region</th>
<th>Carriers Pi*MS</th>
<th>Carriers Pi*MZ</th>
<th>Carriers Pi*SZ</th>
<th>Carriers Pi*ZZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Europe</td>
<td>1,064,350</td>
<td>1,027,452</td>
<td>21,150</td>
<td>11,578</td>
</tr>
<tr>
<td>Central Europe</td>
<td>10,499,896</td>
<td>3,933,048</td>
<td>85,661</td>
<td>17,514</td>
</tr>
<tr>
<td>Belgium</td>
<td>1,043,548</td>
<td>321,642</td>
<td>18,791</td>
<td>2,896</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>20,148,269</td>
<td>3,946,672</td>
<td>262,780</td>
<td>27,515</td>
</tr>
<tr>
<td>Western Europe</td>
<td>5,337,818</td>
<td>1,495,680</td>
<td>71,983</td>
<td>10,146</td>
</tr>
<tr>
<td>North America</td>
<td>18,469,434</td>
<td>7,155,901</td>
<td>257,708</td>
<td>53,173</td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>1,816,658</td>
<td>639,174</td>
<td>28,231</td>
<td>5,476</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>1,669,090</td>
<td>903,232</td>
<td>32,266</td>
<td>10,657</td>
</tr>
<tr>
<td>Africa</td>
<td>17,334,307</td>
<td>1,404,344</td>
<td>75,096</td>
<td>6,412</td>
</tr>
<tr>
<td>Central Asia</td>
<td>6,499,962</td>
<td>4,506,979</td>
<td>40,815</td>
<td>20,504</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>4,063,472</td>
<td>1,605,298</td>
<td>37,898</td>
<td>10,706</td>
</tr>
<tr>
<td>Far East Asia</td>
<td>1,911,276</td>
<td>607,460</td>
<td>3,553</td>
<td>1,771</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>88,814,533</strong></td>
<td><strong>27,225,242</strong></td>
<td><strong>929,014</strong></td>
<td><strong>175,268</strong></td>
</tr>
</tbody>
</table>

Based on AIR data about prevalence in Europe\textsuperscript{14,15,16,17}, it has been estimated that the prevalence of severe AATD in Belgium averages 2600 patients. This estimation originates from a unique Belgian publication concerning neonatal screening for AAT deficiency and 1345 Belgian newborns\textsuperscript{18}. Taking into account the data of the Dutch registry and worldwide estimations, the real Belgian prevalence of ZZ patients can reasonably be estimated at 1600 or 1700 patients. At present, only 40 patients have been diagnosed and registered.

### 10. What is the general management of obstructive lung disease caused by AAT deficiency?

We agree with the management program very recently published in the New England Journal of Medicine\textsuperscript{19}.

#### Evaluation and Management of $\alpha_1$-Antitrypsin Deficiency

<table>
<thead>
<tr>
<th>Initial Evaluation</th>
<th>Follow-up Monitoring</th>
<th>Preventive Therapy</th>
<th>General COPD Treatment</th>
<th>AAT Augmentation Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classify COPD severity</td>
<td>Refer to pulmonologist to monitor lung disease progression</td>
<td>Avoid exposure to respiratory irritants</td>
<td>Per guidelines for non-AAT deficiency COPD</td>
<td>Typically recommended if available</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>Recommend to supplemental oxygen therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history, physical examination</td>
<td>Annual medical history, physical examination</td>
<td>Preventive influenza vaccination</td>
<td>Aggressive treatment of respiratory infections</td>
<td></td>
</tr>
<tr>
<td>Confirm AAT deficiency</td>
<td>Annual full pulmonary-function tests</td>
<td>Limit ethanol intake</td>
<td>Consider only if airflow obstruction, emphysema or both are present</td>
<td></td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Chest radiography</td>
<td>Limit exposure to liver-toxic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary-function tests</td>
<td>Consider baseline chest CT</td>
<td>Limit exposure to respiratory irritants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Discuss family testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest radiography</td>
<td></td>
<td>Consider abdominal ultrasonography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider abnormal ultrasonography</td>
<td></td>
<td>Consider or-biopsy testing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Initial Evaluation

- Exclude other liver diseases
- Evaluate for supplemental oxygen therapy
- Consider abdominal ultrasonography
- Consider or-biopsy testing

#### Follow-up Monitoring

- Refer to hepatologist to monitor liver disease progression
- Consider abdominal ultrasonography
- If there are any signs of liver failure or portal hypertension complications

#### Preventive Therapy

- Avoid ethanol intake
- Avoid exposure to liver-toxic agents
- Avoid obesity and excessive weight gain

#### General COPD Treatment

- Smoking cessation
- Avoid exposure to respiratory irritants

#### AAT Augmentation Treatment

- Consider only if airflow obstruction, emphysema or both are present

Optimal management of stable individuals with AAT deficiency should include many of the interventions recommended for AAT-replete individuals with emphysema, including:

- Inhaled bronchodilators;
- Preventive vaccinations against influenza and pneumococcus;
- Supplemental oxygen when indicated by conventional criteria;
- Pulmonary rehabilitation in individuals with functional impairment;
- Lung transplantation in selected individuals with severe functional impairment and airflow obstruction;
- Management of acute exacerbations including usual therapies for AAT-replete individuals: brief courses of systemic corticosteroids, administration of oxygen and ventilatory support.

when indicated, early antibiotic therapy for all purulent exacerbations, due to the threat of increased elastolytic burden in individuals with AAT deficiency.

11. **Is the efficacy of the augmentation therapy with AAT sufficiently demonstrated?**

Large prospective randomized controlled clinical trials have not been conducted in the past for the following reasons:

- AAT is a rare orphan disease and, surprisingly, only 5 to 10 % of the estimated affected patients have been identified\(^{20}\);
- AAT related lung disease develops slowly over many years;
- A randomized placebo-controlled trial powered to show a difference between AAT and placebo, with a decline in FEV\(_1\) or a reduced mortality as primary endpoints, requires several hundred patients per arm and a follow-up period of 3 to 5 years\(^{21,22}\);

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>target</th>
<th>number of patients</th>
<th>study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowing FEV(_1) decline</td>
<td>21 mL/year 24 %</td>
<td>2 x 213 2 x 164 2 x 143</td>
<td>3 years 4 years 5 years</td>
</tr>
<tr>
<td>Reducing Mortality</td>
<td>40 %</td>
<td>2 x 342</td>
<td>5 years</td>
</tr>
<tr>
<td>Slowing loss in lung tissues</td>
<td>50 %</td>
<td>2 x 65</td>
<td>3 years</td>
</tr>
</tbody>
</table>

Ethical issues have been raised about intravenous treatments with placebo for several years, particularly in countries where the drug has been approved by regulatory agencies. This can also decrease the willingness of patients to participate in such trials.

Thus, a large prospective randomized-controlled study is unlikely to be successful within the next 10 years. Nevertheless, a consistent picture emerges with respect to the effectiveness of the intravenous augmentation therapy from a number of studies.
12. What benefits can be expected from intravenous augmentation therapy with AAT?

- Augmentation infusions increase circulating levels of AAT to levels approximating those seen in heterozygous. A protective level of active AAT is restored in the epithelial lining fluid.

- In efficacy studies, various endpoints have been addressed:
  - slowing the progression of the disease: slowing the decline in FEV\(_1\) (4 cohort studies\(^{23,24,25,26}\), 1 randomized controlled study\(^{22}\), 1 meta-analysis\(^{27}\); slowing the loss in lung tissue (tomodensitometric lung density, 2 randomized control studies\(^{22,28}\));
  - reducing mortality: 1 cohort study\(^{24}\);
  - reducing the frequency of exacerbations: 1 cohort study.

13. What are the indications for augmentation therapy with AAT?

- Only non-smokers or ex-smokers could benefit from augmentation therapy;

- Mainly the group of patients with moderately reduced pulmonary function (FEV\(_1\) of 30-65 % predicted) experience a significant effect from the augmentation therapy on the annual decline in FEV\(_1\) and mortality (ATS/ERS statement 2003). Patients with very poor lung functions, already treated, should be kept on treatment\(^9\);
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Value</th>
<th>Level of Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory testing</td>
<td>AAT serum level &lt; 11 µM or &lt; 50 mg/dL</td>
<td>II-2</td>
<td>Indication for treatment is independent of the phenotype and based on level and presence of obstructive lung disease</td>
</tr>
<tr>
<td>Lung function testing</td>
<td>FEV₁ (post-bronchodilatation) between 30 and 65% predicted</td>
<td>II-2</td>
<td>Subjects with normal or nearly normal pulmonary function can be treated, if they experience a rapid decline in lung function (AFEV₁ &gt;120 ml/yr). Patients with very poor lung function, already treated, should be kept on treatment. Serum level should exceed the 35% predicted threshold, that is, be above 15 µM on Day 7 immediately before the next infusion. If the fourfold dosage of Prolastin is given monthly, the patient is unprotected for several days.</td>
</tr>
</tbody>
</table>

**Dosing and Frequency**

II-3

**Table 3. Augmentation therapy for α₁-antitrypsin deficiency: indication and performance**

- A slower decline of FEV₁, mainly in patients with baseline FEV₁ 30-65 % of predicted, treated with augmentation therapy was confirmed by the recent meta-analysis of Chapman (2009), the decline in FEV₁ having slowed down by 26 %/year or 17.9 mL/year.

The minimum clinically important difference for rate of decline in FEV₁ has not been established in COPD patients. However, investigators involved in the UPLIFT and TORCH studies have suggested that a difference between treatment groups of 15 and 16 mL/year was clinically important.

### Augmentation Therapy for α₁-Antitrypsin Deficiency – Meta-Analysis

- Subjects with normal or near normal lung function can be treated if they experience a rapid decline in FEV₁ (> 120 ml/year).
BTS Recommendations: the working group suggests to initiate a treatment with augmentation therapy in:

- Patients with severe AAT deficiency: AAT level < 50 mg/dL (determined by nephelometry): phenotypes PI*ZZ, PI*Z-null, PI*null-null and some P*SZ;

- Patients with an initial FEV\(_1\) between 30-65% of predicted or a FEV\(_1\) > 65% of predicted and rapid decline of FEV\(_1\) (120 mL/year);

- An initiated treatment must be continued even if the FEV\(_1\) declines below 30% of predicted.

14. How should AAT be administered?

- The FDA approved a dosing schedule of 60 mg/kg/week;

- The studies, which were included in the meta-analysis of Chapman (2009), concerned the effect of AAT augmentation therapy with weekly injections, except for the most important cohort study of the AAT deficiency Registry Study Group (NHLBI Registry, n=1048) which incorporated patients with weekly, bi-weekly and monthly treatments.

- SOY\(^{29}\) searched the optimal therapeutic regimen based on population pharmacokinetics. He showed that 60 mg/kg/week and 120 mg/kg/14 days were enough to obtain sufficient nadir concentrations. 180 mg/kg given every 21 days required AAT monitoring in order to avoid underdosage. Longer intervals were not effective.

Recommendations for Belgium: 60 mg/kg BW/week.

15. What is the cost of AAT augmentation therapy, who will pay for it and what is the cost to the patient?

PROLASTIN 1000 mg, powder and solvent infusion is reimbursed by the Belgian National Service for Medical and Disablement Insurance (RIZIV-INAMI) on the conditions stated in chapter IV bis, and after importation from abroad.
The cost per vial (1000 mg Prolastin) is:

- RIZIV-INAMI cost: €433.03
- Patient cost: €10.80

If we consider an average weight of 67 kg for a woman and 79 kg for a man (Belgian statistics), the patient’s yearly financial participation will be (for 60 mg/kg/week) between €2200 and €2800.

We obtained a grant from the distributing companies Bayer and currently we are receiving funding from Crucell. The personal costs for a patient with no funds may be covered by the Belgian Thoracic Society.

Two major problems persist:

1) The European Medicines Agency (EMEA) encourages the development of medicines for rare diseases – so-called ‘orphan’ medicinal products. AAT deficiency is recognized as an orphan disease (Orphanet). Unfortunately the regulations from EMEA state that the designation of orphan drug status can only be applied “prior” to a compound being licensed for the indication in question. Thus it is no longer possible for PROLASTIN/PULMOLAST to technically receive orphan drug status in Europe.

2) The reimbursement is presently obtained after a report from the medical advisor of the insurance company. Present regulations stipulate only that the patient has to be deficient and to be suffering from a respiratory insufficiency. That is why we insisted on favouring a regulation which restricts the current reimbursement rules, taking into account the phenotype (ZZ, Znull, nullnull, rare SZ) and, according the literature, the FEV1 value (between 30 and 65 % of predicted).

A Commission from RIZIV-INAMI is presently discussing the future reimbursement and conditions for the substitution therapy for AATD in Belgium.

### 16. Cost-benefit issues

The only available analyses looking at cost-effectiveness come from the US. The data comes from the National Institutes of Health (NIH)’s registry.

Hay and colleagues[^30] analyzed the cost per life-year saved (CLYS) for treated individuals. In those cases where Augmentation Therapy was able to improve the patients’ survival by 30-50 percent, the cost-effectiveness for treating them was comparable to widely used, generally accepted, medical interventions such as antihypertensive, oestrogen therapy for postmenopausal women, coronary bypass and cholesterol-lowering drugs. The published data from the NHLBI indicates an improved survival of 36 percent.

Alkins & al.[^31] calculated the incremental cost per year of life saved for AAT replacement therapy. The survival advantage in AAT deficient subjects, with an initial FEV1 lower than 50 % predicted, equated to 55 % efficacy. The incremental cost per year of life saved for AAT replacement therapy was €10,000 ($13,971). The authors concluded that AAT replacement therapy was cost-effective in patients with severe AAT deficiency and severe COPD (FEV1 < 50 % of predicted).
The cost-effectiveness was comparable to renal dialysis and better than the use of simvastatin for primary prevention of coronary artery disease and mammography screening for breast cancer every 18 months in women aged 40 to 49 years.

The third analysis looking at cost-effectiveness was less favourable. Gildea and collaborators\textsuperscript{32} used a model of disease progression and concluded that the incremental cost-effectiveness ratio was €148,460 (\$207,841)/QALY for replacement therapy until FEV1 drops below 35 \% predicted and €223,200 (\$312,511)/QALY for an augmentation for life strategy. Compared to other conventionally-used health interventions, augmentation was “relatively less cost-effective” but augmentation therapy remained “the only specific therapy that is currently available for individuals with severe AAT Deficiency”.

**References**

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