

VISION ACADEMY VIEWPOINT

The Vision Academy is a partnership between Bayer and ophthalmic specialists, established with the aim of addressing key clinical challenges in the field of retinal diseases: www.visionacademy.org.

Defining Non-Adherence and Non-Persistence to Anti-VEGF Therapies in nAMD

Background

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are a safe and effective treatment option for patients with neovascular age-related macular degeneration (nAMD),^{1,2} but frequent injections and close follow-up are necessary to minimize vision loss.^{1,3} Real-world evidence suggests that despite the design of more flexible dosing regimens to minimize treatment burden, discrepancies between outcomes in clinical trials and those seen in clinical practice persist due to non-adherence (lack of adherence to clinical trial regimens) or non-persistence (undertreatment).^{3,4}

A systematic review conducted by the nAMD Barometer Leadership Coalition of the risk factors for non-adherence and non-persistence to intravitreal anti-VEGF treatment in nAMD found that the prevalence of non-adherence to treatment ranged from 32% to 95%, while up to 60% of patients stopped treatment by 24 months.³ Although risk factors are multifaceted, both patient- (e.g., systemic comorbidities and distance to treatment center) and clinic-related factors (e.g., changes in reimbursement criteria and capacity constraints) were found to have an impact, while treatment efficacy was reported as a protective factor.³ The review also highlighted the need for standardization in the definitions of both non-adherence and non-persistence in order to better assess the extent of these issues.

To address this need, an additional systematic review was performed to identify commonly used terminology. The results informed the development of definitions and a classification system for the factors associated with non-adherence and non-persistence to anti-VEGF treatment in nAMD. These definitions were validated, using a modified Delphi approach, by the nAMD Barometer Leadership Coalition and subsequently endorsed by retinal experts from the Vision Academy.⁴ The resulting framework for assessing treatment non-adherence and non-persistence over time and across different health settings aims to improve understanding to optimize outcomes in patients with nAMD.

Developed by the nAMD Barometer in
September 2021

Viewpoint

To ensure consistency when assessing the prevalence of non-adherence and non-persistence to anti-VEGF therapies in nAMD, a single definition was developed for each term. The validated definitions outlined in the tables below use attendance at any scheduled clinic visit (both monitoring and injection visits) as measures of adherence and persistence, thereby allowing the terminology to be used across different injection regimens and practice settings.

Adherence⁴

Term	Definition
Full adherence	Attendance at every scheduled clinic visit and undergoing every treatment or monitoring procedure advised by the treating physician over 12 months
Adherence	Missing ≤ 1 treatment or monitoring visit scheduled as advised by the treating physician over 12 months ^{a,b}
Non-adherence	Missing ≥ 2 treatment or monitoring visits scheduled as advised by the treating physician over 12 months ^{a,b}

^aA visit is considered missed if the recommended appointment date is exceeded by >2 weeks for any reason. The number of missed visits is determined based on the potential visits missed during the non-adherent period, using the last recommended visit interval; ^bThe period of 12 months begins from the time of the first injection. For subsequent years of treatment, adherence is calculated every 12 months.

Adherence was split into “full adherence” and “adherence” to offer a gradient between binary adherence and non-adherence, with “adherence” offering a less stringent definition that is more achievable in clinical practice. Adherence was defined as missing no more than one appointment over a 12-month period based on a first-year treat-and-extend regimen, as a $>80\%$ cut-off is commonly reported as constituting good adherence to general medications.^{5,6} For patients with bilateral nAMD, adherence is assessed using the eye with the shortest visit interval.⁴

Persistence⁴

Term	Definition
Persistence	Maintaining treatment or monitoring as advised by the treating physician and attending the most recent appointment within the last 6 months ^a
Non-persistence	Not attending any treatment or monitoring visits for any reason within the last 6 months or not scheduling follow-up appointments for any reason for 6 months ^b

^aA patient is not required to be adherent to be persistent; ^bThe first day of the 6-month period after the most recent appointment attended should serve as the date of onset of non-persistence. A minimum of 6 months since the first injection is required to assess persistence.

The 6-month non-attendance cut-off was chosen to capture patients who have the largest extensions between treatments (4 months), while reflecting the fact that almost all patients would require a treatment or monitoring visit within this time period. Due to the minimum period of 6 months necessary to assess persistence, a patient can be considered persistent while not being adherent, but not vice versa.

Vision Academy Viewpoints are intended to raise awareness of a clinical challenge within ophthalmology and provide an expert opinion to engage in further discussion.

They can be downloaded from <https://www.visionacademy.org/resources>

The Vision Academy is sponsored by Bayer. This document was prepared by Tariq Aslam, Jane Barratt, Vincent Daien, Bora Eldem, Robert Finger, Richard Gale, Laurent Kodjikian, Xiaofeng Lin, Anat Loewenstein, Paul Mitchell, Mali Okada, Francisco Rodríguez, Jude Stern, James Talks, David Wong, Tien Yin Wong, and Focke Ziemssen, all of whom are members of the nAMD Barometer Leadership Coalition and/or of the Vision Academy.

Always refer to local treatment guidelines and relevant prescribing information. The views represented in this document do not necessarily reflect those of Bayer.

References

1. Bakri SJ, Thorne JE, Ho AC *et al.* Safety and efficacy of anti-vascular endothelial growth factor therapies for neovascular age-related macular degeneration: a report by the American Academy of Ophthalmology. *Ophthalmology* 2019; 126 (1): 55–63.
2. Solomon SD, Lindsley K, Vedula SS *et al.* Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev* 2014; 8 (8): CD005139.
3. Okada M, Mitchell P, Finger RP *et al.* Nonadherence or nonpersistence to intravitreal injection therapy for neovascular age-related macular degeneration: a mixed-methods systematic review. *Ophthalmology* 2021; 128 (2): 234–247.
4. Okada M, Wong TY, Mitchell P *et al.* Defining nonadherence and nonpersistence to anti-vascular endothelial growth factor therapies in neovascular age-related macular degeneration. *JAMA Ophthalmol* 2021; 139 (7): 769–776.
5. Glombiewski JA, Nestoriuc Y, Rief W *et al.* Medication adherence in the general population. *PLoS One* 2012; 7 (12): e50537.
6. Malta M, Strathdee SA, Magnanini MMF *et al.* Adherence to antiretroviral therapy for human immunodeficiency virus/acquired immune deficiency syndrome among drug users: a systematic review. *Addiction* 2008; 103 (8): 1242–1257.
7. Sabaté E. Adherence to long-term therapies : evidence for action (2003) (E. Sabaté Ed.). Geneva: World Health Organization.
8. Ehliken C, Helms M, Böhringer D *et al.* Association of treatment adherence with real-life VA outcomes in AMD, DME, and BRVO patients. *Clin Ophthalmol* 2018; 12: 13–20.

Planned discontinuation and transfer of care⁴

Term	Definition
Planned discontinuation	Lack of treatment response (treatment futility) or no disease activity requiring ongoing treatment, as judged by the treating physician
Transfer of care	The ongoing management of a patient's nAMD, transferred to another physician

The term “planned discontinuation” accounts for patients who intentionally choose to discontinue treatment. Patients are still considered persistent if they attend visits with other physicians or clinics for the purpose of monitoring or treating their nAMD. “Transfer of care” is when a patient is known to have followed up with another physician but treatment details are unknown.⁴

Factors affecting non-adherence and non-persistence

The World Health Organization describes five interacting dimensions that affect patient adherence.⁷ The following classification, based on the World Health Organization dimensions, covers all injection regimens used in nAMD but is restricted to anti-VEGF therapy for nAMD only. This is because intravitreal treatment is often more time-critical in nAMD⁴ and reasons for non-adherence or non-persistence are likely to differ in this population compared to those with other retinal diseases.⁸

Dimension ^a	Subcategories
Patient-associated	<ul style="list-style-type: none"> • Education level or understanding of the need for treatment • Loss of motivation • Ocular comorbidities • Non-ocular comorbidities or general health problems • Consent withdrawal • Treatment burden • Other
Condition-associated	<ul style="list-style-type: none"> • Treatment success (patient-determined) • Treatment failure (patient-determined) • Treatment contraindication • Poor baseline visual acuity • Other
Therapy-associated	<ul style="list-style-type: none"> • Treatment discomfort • Adverse events • Fear of injections • Other
Health system and healthcare team-associated	<ul style="list-style-type: none"> • Administrative problem • Access to treatment (e.g., appointment availability) • Distance to treatment • Other
Social/economic-associated	<ul style="list-style-type: none"> • Lack of transportation • Caregiver availability (e.g., to attend clinic appointment with patient) • Direct cost or reimbursement issue • Indirect costs (e.g., parking fees, productivity loss) • Other
Other	<ul style="list-style-type: none"> • Death • Uncontrollable/unpredictable event (e.g., restrictions or deferral of appointment due to COVID-19 pandemic)

^aThe five dimensions affecting patient adherence were originally described by the World Health Organization.⁷

Further considerations

These definitions are based on consensus opinions and are yet to be tested on patient data sets. As the classification system was established in the setting of an industry-sponsored group, which could mean subconscious bias was introduced in the recommendations, the clinical relevance of the proposed system will be examined in the next phase of the nAMD Barometer initiative.⁴ Further studies are required to address the lack of available data assessing the effectiveness of different strategies to improve treatment adherence and persistence to intravitreal therapy in nAMD.³ Future work could determine whether the identification of high-risk individuals can modify outcomes, with the aim of developing meaningful interventions.⁴

Vision Academy Viewpoints are intended to raise awareness of a clinical challenge within ophthalmology and provide an expert opinion to engage in further discussion.

They can be downloaded from <https://www.visionacademy.org/resources>

The Vision Academy is sponsored by Bayer. This document was prepared by Tariq Aslam, Jane Barratt, Vincent Daien, Bora Eldem, Robert Finger, Richard Gale, Laurent Kodjikian, Xiaofeng Lin, Anat Loewenstein, Paul Mitchell, Mali Okada, Francisco Rodríguez, Jude Stern, James Talks, David Wong, Tien Yin Wong, and Focke Ziemssen, all of whom are members of the nAMD Barometer Leadership Coalition and/or of the Vision Academy.

Always refer to local treatment guidelines and relevant prescribing information.

The views represented in this document do not necessarily reflect those of Bayer.

September 2021 | MA-PFM-OPHT-ALL-0599-1