

Effect of Adherence to Hemophilia Drug Therapy on Outcomes: A Systematic Literature Review

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BACKGROUND

- Hemophilia A (HA) and B (HB) are X-linked, inherited bleeding disorders caused by deficiency of factor VIII or factor IX, respectively.¹
- Although the advantages are well established for clotting factor replacement therapy in patients living with hemophilia, the degree of treatment adherence may impact these benefits.
- Treatment adherence may be challenging due to the mode of administration and frequency of self-administered injections or infusions, particularly among patients receiving prophylactic therapy.

OBJECTIVE

- This systematic literature review (SLR) aimed to investigate the effect of adherence to hemophilia treatment on clinical, humanistic, and economic outcomes.

METHODS

- Literature searches were conducted in Embase, MEDLINE and MEDLINE In-Process, and Cochrane Library for English-language articles published from 22 June 2013 through 22 June 2023.
- Bibliographies of included studies also were searched for additional publications.
- Articles were screened for eligibility by 2 independent reviewers at abstract and full-text levels.
- This review included observational and qualitative studies.

RESULTS

- 20 articles were included after screening 722 citations.
- The studies examined relationships between treatment adherence and bleeding, joint health, inhibitor development, pain, quality of life (QOL), daily activity/work productivity, cognitive function, and healthcare resource use.
- 15 studies found that better adherence to hemophilia treatment is associated with clinical (Table 1), humanistic (Table 2), and economic (Table 3) outcomes, including the following:
 - Reduced bleeding risk, better joint structure and function, decreased chronic pain, and improved cognitive function²⁻¹¹
 - Reduced activity impairment and improved health-related QOL (HRQOL)^{7,12-16}
 - Less school/work absenteeism and greater work productivity^{2,5,15,16}
- Significant differences in mean QOL scores were observed between suboptimally adherent and adherent patients (74.1 vs. 81.2; $P < 0.050$).⁷
- The remaining articles reported no association between adherence and bleeding, with one reporting better outcomes in nonadherent patients.
- Heterogeneity across identified studies prevented meta-analysis.

CONCLUSIONS

- This SLR demonstrated associations between increased adherence to hemophilia treatment, specifically factor replacement therapy, and improved outcomes, suggesting that improvements in adherence would benefit patients.
- Future hemophilia treatment options that require administration of a single dose that are administered subcutaneously or involve less frequent dosing regimens may improve health outcomes by improving adherence.

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Table 1. Effect of Adherence on Clinical Outcomes			
Author, year (country)	Population (age, mean [SD])	Treatment adherence	Association with outcomes
Poor adherence associated with increased bleeding			
García-Dasí et al., 2015 ⁷ (Spain)	Children and adolescents: severe HA (N = 78) • 11.9 (3.9) years	• AAI range (mean, SD): -64.4 to 66.7 (-3.08 to 14.4) • Infra-adherent, ^a n (%): 26 (33.3) • Adherent, ^b n (%): 41 (52.6) • Over adherent, ^c n (%): 11 (14.1)	Mean no. of bleeding episodes: • Adherent, 1.4 • Infra-adherent, 4.5 ($P < 0.010$)
Dover et al., 2020 ⁶ (Canada)	Children: severe HA (N = 56) • Median (ROV): 1.63 (1-2.5) years	• Overall median (ROV) adherence with prophylaxis: 85.7% (37.4%-99.8%) weeks per patient • Overall median (ROV) adherence with enhanced episodic therapy protocol: 47.1% (0%-100%) per patient	Over any 12-week period: 10% increase in absolute adherence rate corresponded with a 15% reduction in bleeding rate (HR, 0.85; 95% CI, 0.81-0.90)
Lambert et al., 2021 ³ (Côte d'Ivoire)	Pediatric: severe (n = 24) and moderate (n = 1) HA or HB • 5.6 (2.5) years	Adherence, n (%): 7 (29)	• Difference in ASJBR for adherent vs. nonadherent: $P = 0.0063$
Mokhtar et al., 2021 ⁴ (Malaysia)	Adults: severe HA or HB (N = 103) • 33.13 (11.91) years	Mean (SD) VERITAS-Pro ^d scale scores pre-HMTAC: • Total score: 48.01 (13.684) Mean (SD) VERITAS-Pro scale scores post-HMTAC: • Total score: 38.03 (9.848)	• Mean ABR: – Adherent, 94.2% – Nonadherent, 5.8% • Mean (SD) bleeding rate: – Adherent, 3.91 (3.99) – Nonadherent, 7.67 (7.37); $P = 0.005$ Dose and Remember subscales: • Significant relationships between adherence with ABR, with P values of 0.025 and 0.018, respectively
Zupan et al., 2023 ⁸ (Slovenia)	Mild (n = 11), moderate (n = 9), and severe (n = 43) HA • Range: ≤ 11 to ≥ 61 years	26 of 56 respondents (46.4%) reported that they had missed, forgotten, or delayed their scheduled doses at some point in the past	Mean no. of bleeds in past 12 months: • Nonadherent, 5.9 • Adherent, 4.6
Krishnan et al., 2015 ² (US, Canada, and Australia)	Adults: moderate or severe HA or HB (n = 55) • NR	• Nonadherence to prophylaxis (VERITAS-Pro ^d <57), n (%): – Adherent: 41 (74.5) – Nonadherent: 14 (25.5)	Worse adherence associated with: • More breakthrough bleeds (B = 0.047; $P < 0.01$) • More target joint bleeds in prior year (B = 0.055; $P < 0.01$)
Adherence associated with better joint health			
Zanon et al., 2020 ⁵ (Italy)	Severe HA (N = 40) • NR	Level of adherence, n (%): • None: 4 (10) • Minimal: 4 (10) • Low: 4 (10) • Medium: 9 (22.5) • High: 19 (47.5)	• No. of total target joints declined for adherent patients • Mean (SD) HJHS* decreased in adherent patients from 2.3 (3.2) to 0.1 (0.4) • Physical activity: highly adherent patients did more sports and engaged in more physical activities vs. patients with no or low adherence
Zhao et al., 2022 ⁹ (China)	Severe HA (n = 17) • Median (range): 22 (4-41) years	Mean VERITAS-Pro ^d scale scores: • Time: 11.2 • Dose: 8.9 • Plan: 8.3 • Remember: 10.2 • Skip: 9.0 • Communicate: 12.1	• VERITAS-Pro scores: – HEAD-US-C score ($r = 0.49$; $P = 0.046$) – HJHS ($r = 0.64$; $P = 0.005$) • Indicates better adherence to prophylaxis was favorable for joint protection
Adherence associated with lower likelihood of high chronic pain levels			
McLaughlin et al., 2014 ¹⁰ (US)	Adolescents and young adults: HA or HB • Range: – 13-17 years (n = 41) – 18-25 years (n = 39)	• Mean (SD) VERITAS-Pro ^d (n = 69): 49.6 (12.9) • Mean (SD) VERITAS-PRN (n = 11): 51.0 (11.6)	High chronic pain level: • Higher combined [†] VERITAS (Pro and PRN): mean (SD) scores 53.1 (12.0) vs. 48.0 (12.8); $P = 0.08$ Low levels of self-reported chronic pain: • $P < 0.05$ Prophylactic patients: • Mean VERITAS-Pro scores: – High chronic pain: 53.6 (12.3) – Low chronic pain: 47.4 (12.9); $P = 0.05$
Adherence associated with better cognitive function			
Cheung et al., 2023 ¹¹ (Hong Kong)	Pediatric patients (n = 11), young adults (n = 22), and adults (n = 9): mild, moderate, or severe HA or HB • Median (IQR): – 15.6 (13.4-16.6) years – 33.0 (26.4-36.9) years – 55.2 (50.9-56.8) years	VERITAS-Pro ^d Adults: • Nonadherence median (IQR): 65 (54-76.5) Young adults: • Nonadherence median (IQR): 61 (53-67) Pediatric patients: • Nonadherence median (IQR): 47 (45-57)	Prophylactic treatment (71.4%) medication adherence correlated with: • Attention ($P = 0.024$) • Cognitive flexibility ($P = 0.037$)

^a Infra-adherents were patients who were administered less than prescribed. ^b Adherents were patients who were administered as prescribed. ^c Over adherents were patients who were administered more than prescribed. ^d VERITAS-Pro scores: range, 24-120; higher scores indicate worse adherence. ^e HJHS: range, 0-20 per joint; lower scores represent better joint status. [†] Logistic regression showed: For each 10-point decrease in combined VERITAS (Pro and PRN) scores, there was a 35% (OR, 0.65; 95% CI, 0.44-0.96; $P = 0.03$) and 39% (OR, 0.61; 95% CI, 0.39-0.96; $P = 0.03$) decrease in likelihood of having high chronic pain, respectively. Note: All patients received prophylaxis and/or on-demand treatment. Age values are mean (SD) unless otherwise noted. AAI = Absolute Adherence Index; ABR = annualized bleeding rate; ASJBR = annual spontaneous joint bleeding rate; B = unstandardized beta; CI = confidence interval; HEAD-US-C = Hemophilic Early Arthropathy Detection with UltraSound in China; HJHS = Hemophilia Joint Health Score; HMTAC = Hemophilia Medication Therapy Adherence Clinic; HR = hazard ratio; IQR = interquartile range; NR = not reported; OR = odds ratio; ROV = range of values; SD = standard deviation; US = United States; VERITAS-Pro = Validated Hemophilia Regimen Treatment Adherence Scale–Prophylaxis; VERITAS-PRN = Validated Hemophilia Regimen Treatment Adherence Scale–On-Demand.

Table 2. Effect of Adherence on Humanistic Outcomes			
Author, year (country)	Population (age, mean [SD])	Treatment adherence	Association with outcomes
García-Dasí et al., 2015 ⁷ (Spain)	Children and adolescents: severe HA (N = 78) • 11.9 (3.9) years	• AAI range (mean, SD): -64.4 to 66.7 (-3.08 to 14.4) • Infra-adherent, ^a n (%): 26 (33.3) • Adherent, ^b n (%): 41 (52.6) • Over adherent, ^c n (%): 11 (14.1)	Differences in QOL scores: • Adherent vs. infra-adherent ($P < 0.050$) • Adherent vs. over adherent ($P = 0.985$) AAI and the Feelings, View, Family, Sport and School, Coping, and Treatment subscales: • $P < 0.05$
Torres-Ortuño et al., 2018 ¹⁴ (Spain)	Severe hemophilia (N = 23) • 31.96 (11.81) years	• ≤ 62 points (adherent) on VERITAS-Pro ^d = 10 (43.5%) • > 62 points (nonadherent) on VERITAS-Pro = 13 (56.5%)	Higher QOL in adherent patients: • Pain (ES = 0.85) • Vitality (ES = 0.78) • Physical Health (ES = 0.80) • Emotional Functioning (ES = 0.88) • Better overall health ($P < 0.01$)
Shaikh et al., 2022 ¹³ (Europe)	Severe HA or HB (N = 514) • 37.5 (15.0) years	• Low/medium, n (%): 202 (39) • High, n (%): 312 (61)	• EQ-5D ^e scores were higher for patients with high overall treatment adherence (vs. low/medium) • High vs. low/medium adherence was associated with a 0.06 increment in EQ-5D utility score
Cheung et al., 2022 ¹⁶ (Hong Kong)	Adults (n = 42) and pediatric patients (n = 14): mild, moderate, or severe HA or HB • Mean (SD) [range]: – 37.2 (14.5) [17.5-68.4] years – 10.0 (2.8) [5.2-15.1] years	Adults: • Mean (SD) VERITAS-Pro ^d scale scores: – Overall: 63.7 (13.8) Pediatric patients: • Mean (SD) VERITAS-Pro scale scores: – Overall: 43.3 (10.2)	Skipping prophylactic treatment: • Worse self-perception ($r = 0.32$; $P = 0.044$) • Worse functioning in sports and leisure ($r = 0.31$; $P = 0.033$)
Bago et al., 2021 ¹² (Croatia and Slovenia)	Severe or moderate HA (n = 70) or HB (n = 12) • Median (range): 44.50 (18-73) years	Mean reported VERITAS-Pro ^d adherence score: 42 • Adherent: 83%	Medication nonadherence associated with poorer health: • Bodily Pain domain ($r = -0.24$; $P = 0.033$) • MCS ($r = -0.26$; $P = 0.019$) Bodily Pain and Social Functioning domains and MCS: • Medication adherence associated with better HRQOL • Mental Health domain, adherence ($P = 0.059$)
O'Hara et al., 2021 ¹⁵ (France, Germany, Italy, Spain, and UK)	Adults: severe HA (N = 376) • 37.2 (14.7) years	• Low/medium, n (%): 139 (37.0) • High n (%): 237 (63.0)	High adherence associated with: • Reduced activity impairment vs. low/medium adherence ($P = 0.012$)

^a Infra-adherents were patients who were administered less than prescribed. ^b Adherents were patients who were administered as prescribed. ^c Over adherents were patients who were administered more than prescribed. ^d VERITAS-Pro scores: higher scores indicate worse adherence. ^e EQ-5D score: higher scores indicate better health. Note: All patients received prophylaxis and/or on-demand treatment. Age values are mean (SD) unless otherwise noted. ES = effect size; MCS = Mental Component Summary; UK = United Kingdom.

Table 3. Effect of Adherence on Economic Outcomes			
Author, year (country)	Population (age, mean [SD])	Treatment adherence	Association with outcomes
Zanon et al., 2020 ⁵ (Italy)	Severe HA (N = 40) • NR	Level of adherence, n (%): • None: 4 (10) • Minimal: 4 (10) • Low: 4 (10) • Medium: 9 (22.5) • High: 19 (47.5)	Mean (SD) no. of school/workdays lost: • Adherent, 3.4 (6.8) to 0.2 (0.9) • Nonadherent, 8.5 (12.6) to 2.8 (4.0)
O'Hara et al., 2021 ¹⁵ (France, Germany, Italy, Spain, and UK)	Adults: severe HA (N = 376) • 37.2 (14.7) years	• Low/medium, n (%): 139 (37.0) • High n (%): 237 (63.0)	High adherence associated with: • Reduced WPL vs. low/medium adherence ($P = 0.012$)
Krishnan et al., 2015 ² (US, Canada, and Australia)	Pediatric patients: moderate or severe HA or HB (n = 55) • NR	• Nonadherence to prophylaxis (VERITAS-Pro ^a < 57), n (%): – Adherent: 51 (92.7) – Nonadherent: 4 (7.3)	• Worse adherence associated with more days of work or school missed due to bleeding (B = 0.072; $P < 0.01$)

^a VERITAS-Pro scores: range, 24-120; higher scores indicate worse adherence. Note: All patients received prophylaxis and/or on-demand treatment. Age values are mean (SD) unless otherwise noted. WPL = work productivity loss.