HIV-associated wasting prevalence in the era of modern antiretroviral therapy

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Objective: To understand the prevalence of HIV-associated wasting (HIVAW) in the United States.

Design: Medical and pharmacy claims study using IBM MarketScan Commercial, Medicare Supplemental and Medicaid Databases.

Methods: Study period: July 2012–September 2018 (first HIV diagnosis claim = HIV index date). People with HIV (PWH) were excluded if they were aged less than 18 years, had any malignancy claim or had less than 6 months of enrollment data pre or post-HIV index date. HIVAW was defined by proxy using claims for weight loss–related diagnoses, appetite stimulant/nontestosterone anabolic agents or enteral/parenteral nutrition. Prevalence was reported cumulatively, by insurance type and antiretroviral therapy (ART) pharmacy claims (defined as ≥1 pharmacy claim of any ART within 12 months post-HIV index date). Statistical analysis assessed factors potentially associated with HIVAW.

Results: The study population comprised 42,587 PWH (64.6% male, mean age 44 years, 67.5% on Medicaid, 63.9% on ART). Cumulative HIVAW prevalence (2012–2018) was 18.3% (n = 7804) for all PWH (17.9% on ART, 19.1% not on ART). HIVAW prevalence by payer was 7.5% for Commercial and Medicare Supplemental and 23.5% for Medicaid. The strongest associations with the likelihood of meeting the definition of HIVAW were for individuals with Medicaid and hospitalization(s) post-HIV index date; race and ART status were not associated.

Conclusions: Findings suggest HIVAW remains prevalent in PWH. ART use was not found to be associated with HIVAW. HIVAW was highest among those with Medicaid coverage or any hospitalization(s). Further research is needed to better understand additional factors associated with and contributing to HIVAW.

Introduction

Advances in antiretroviral therapy (ART) and the care of people with HIV (PWH) have improved AIDS-associated morbidity and mortality [1,2]. However, as PWH are living longer, they remain at higher risk of age-associated comorbidities including HIV-associated wasting (HIVAW) [1,3]. HIVAW increases morbidity and mortality but has...
received little attention in the era of modern ART [4,5]. HIVAW etiology can be multifactorial and may include any of the following: poverty and food insecurity, dysphagia, anorexia, depression, substance use, diarrhea and malabsorption disorders, chronic infection, malignancy, hormonal imbalances, metabolic changes, and cytokine excess [6–8]. In 1987, the US Centers for Disease Control and Prevention (CDC) classified HIVAW as an AIDS-defining condition, defined by involuntary weight loss accompanied by chronic diarrhea, fever, and weakness for 30 days without an underlying etiology [6]. Indeed, HIVAW was a frequent AIDS-defining condition during the early years of the HIV epidemic [6]. Today, HIVAW is commonly defined as unintentional loss of body weight or lean body mass, as well as reduction in physical endurance and overall function [4,7].

The widespread use of ART has not eliminated the incidence of wasting in PWH. In a study by Tang et al. [5], it was observed that for every 1% loss in weight, there was an 11% increase in the risk of death. When weight loss was at least 10% from baseline weight, the relative risk of mortality was increased nearly six-fold. Additionally, the Multicenter AIDS Cohort Study (2016) showed that prior to the end of 2003, median survival was markedly lower among HIV-infected men with wasting (9.1 years; 95% confidence interval [CI] 8.4–9.6 years) compared with HIV-infected men with no history of wasting (11.6 years; 95% CI 11.0–12.4 years) [4].

In 2009, Siddiqui et al. [9] conducted a database analysis of healthcare claims data for commercial health plan enrollees with evidence of HIV infection to estimate the prevalence and burden of HIVAW. An algorithm incorporating diagnosis and procedure claim markers of weight loss was developed by clinical and coding experts to identify patients with evidence of HIVAW. Among 12,187 continuously enrolled patients with HIV between January 2005 and July 2007, 1,006 (8.3%) had evidence of HIVAW. Patients with evidence of HIVAW were older (44.1 vs. 42.6 years) and more commonly male than female (8.8% vs. 5.3%). Additionally, several comorbidities were statistically more common in the HIVAW cohort vs. non-HIVAW cohort, including dyslipidemia, depression, and chronic airway disease. The authors concluded that, despite effective ART use, almost one in 10 PWH enrolled in managed care had evidence of HIVAW [9].

To the best of our knowledge, there have been no studies evaluating the prevalence of HIVAW since 2009. The objective of this database analysis of medical and pharmacy claims was to evaluate the prevalence and comorbidity burden of HIVAW across US payer types (2012–2018).

**Methods**

This analysis of the IBM MarketScan Commercial, Medicare Supplemental and Multi-State Medicaid Research Databases included data from July 2013 to March 2019 for the Commercial and Medicare Supplemental data, and from July 2012 to December 2018 for the Medicaid data.

The Commercial Database consists of medical and pharmacy claims data from employers and health plans. It contains data for more than 30 million employees, their spouses and dependents who are covered by employer-sponsored private health insurance in the United States. The Medicare Supplemental Database includes retirees with Medicare supplemental insurance paid by employers. The Multi-State Medicaid Database contains the medical, surgical and prescription drug experience of more than 47 million enrollees. All data sets include patient-level data on enrollment, inpatient services, outpatient services and prescription drug claims. Upon enrollment, patients are assigned a unique identifier, allowing for a unique sample of patients. Standard demographic variables are also included; however, the inclusion of some patient characteristics is not uniform among the databases. For example, the Commercial and Medicare Supplemental Databases include geographic location, whereas the Medicaid Database includes patient race and ethnicity. As this was an analysis of existing medical and pharmacy claims data and no patient-identifiable information was included in the claims data set, institutional review board approval was not required.

**People with HIV study population**

The PWH study population comprised patients with a diagnosis of HIV using the International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) codes for HIV (042 [ICD-9-CM] or B20 [ICD-10-CM]) between July 2012 and September 2018. Patients were excluded if they were less than 18 years of age, had a diagnosis claim for any malignancy or had less than 6 months of enrollment data pre or post-HIV index date. The HIV index date was defined as the first HIV diagnosis date between July 1, 2012 and September 30, 2018 (Fig. 1).

The PWH study population was divided into two cohorts: HIVAW and non-HIVAW. There is no specific ICD-9-CM/ICD-10-CM code for HIVAW; therefore, a modified version of a previously developed and published algorithm specific to claims data was used to identify patients meeting a definition for HIVAW (see footnote b in Table 1) [9]. Patients in the HIVAW cohort must have met at least one of four criteria (A, B, C, D; Table 1). The non–HIVAW cohort included those who did not meet the definition of HIVAW in the study period.

**Measures**

The cumulative prevalence of HIVAW was calculated as the proportion of PWH meeting the definition for HIVAW between July 2012 and September 2018 divided
by the total number of PWH included in the study during the same time period. Patient demographics included age, sex, geographic location (Commercial and Medicare Supplemental population only), race (Medicaid population only) and insurance type at HIV index date. Clinical characteristics were assessed in the 6-month pre–HIV index period and comprised the Charlson Comorbidity Index (CCI) [10], selected metabolic and mental health conditions, opportunistic infections and selected HIV/AIDS conditions. The CCI is a validated health status assessment based on diagnostic codes and weights for 17 comorbidities, and is reported as a summary score [10]. Two conditions were not included in the calculation: HIV/AIDS, because all patients had the condition, and cancer/malignancy, because PWH were excluded if they had a cancer/malignancy diagnosis (as causality of wasting prevalence).

**Table 1. Identification of the PWH study population and HIV-associated wasting cohort.**

| Study population: PWH | N = 196,297 |
|-----------------------|-------------|
| Total patients with HIV diagnosis between 1 July 2012 and 30 September 2018 | N = 196,297 |
| Inclusion | ≥2 outpatient claims (>30 days apart) or ≥1 inpatient claim for HIV |
| Inclusion | ≥18 years old on the HIV index date |
| Exclusion | Patients with any malignancies |
| Inclusion | Patients continuously enrolled for ≥6 months pre and post-HIV index date |
| **Cohort: HIVAW** | PWH study population, N = 42,587, n (%) |
| **A. ≥1 inpatient claim or ≥2 outpatient claims (with same diagnosis code on different service date or combination of any diagnosis below on different dates) with a diagnosis for weight loss** | 6873 (16.1) |
| **B. A claim for appetite stimulant or nontestosterone anabolic agent** | Appetite stimulants (dronabinol, megestrol), and anabolic agents (oxandrolone, nandrolone, oxymetholone, DHEA, 7-oxo-DHEA, androstenedione) |
| **C. Evidence of enteral or parenteral nutrition** | Enteral infusion of nutritional substances, enteral nutrition home therapy, enteral feeding supplies, enteral nutrition formula/additives, enteral nutrition infusion pump, total parenteral nutrition home therapy, parenteral nutrition solution additives, parenteral nutrition supplies, parenteral nutrition infusion pump, amino acid injections/solutions (Aminosyn, FreAmine, ProcalAmine, TRAVASOL) |
| **D. At least two of the following:** | Presence of only one medical claim for weight loss or wasting in the primary or secondary position; anorexia (≥1 inpatient claim or ≥2 outpatient claims at least 30 days apart), a claim for testosterone (and derivatives), growth hormone, thalidomide, or high-calorie nutritional supplements |
| **Total HIVAW cohort** | 7804 (18.3) |

Criteria requiring two or more outpatient diagnosis claims were required to be on separate service dates. BMI, body mass index; DHEA, dehydroepiandrosterone; HIV/A, HIV-associated wasting; PWH, people with HIV.

*Patients might have met more than one criterion.

**The current study used an inclusion of ≥1 inpatient claim or ≥2 outpatient claims for weight loss diagnosis, whereas Siddiqui 2009 only included two or more medical claims (inpatient or outpatient).**

**Fig. 1. Study period.** aDefined as first date that all criteria were met between 1 July, 2012 and 30 September, 2018. b2012–2013 includes Medicaid only; 2019 includes Commercial and Medicare Supplemental through March only. HIVAW, HIV-associated wasting.
cachexia either from cancer/malignancy or from HIV infection could not be distinguished. The opportunistic infections and selected HIV/AIDS conditions required one or more claim. In addition, two or more claims for testing CD4\(^+\) cell count and/or HIV viral load within the 9 months pre and post-HIV index date were evaluated to serve as a proxy for receiving regular care/monitoring. This is consistent with CDC guidelines, which use a similar measure to define ‘retained care’, which is two or more claims for CD4\(^+\) cell count or viral load three or more months apart within 1 year [11].

Evidence of prescribed ART was defined as having ≥1 pharmacy claim for any ART within the 12 months post-HIV index date, based on a National Quality Forum HIV quality measure [12]. The type of ART was categorized as combination ART (cART), single-tablet regimen (STR) or single ART. cART was defined as claims for two or more single antiretroviral agents or fixed-dose products containing two or more single antiretroviral agents.

Factors potentially correlated with HIVAW were included as covariates in the statistical models. Variables were included in models if they had an unadjusted \(P\)-value ≤0.1 for the difference between cohorts or were selected \textit{a priori} from literature reviews and expert opinions. The final covariates measured during the pre-HIV index period that provided the best fit model were age (in years at HIV index date), sex, race (Medicaid population only), insurance type (Commercial and Medicare Supplemental vs. Medicaid), CCI and having one or more opportunistic infection or selected HIV/AIDS condition. Other covariates were included, if information was available post-HIV index date, as follows: duration of follow-up from HIV index date, two or more claims for testing CD4\(^+\) cell counts and/or viral load in the 9 months pre and post-HIV index date, one or more pharmacy claims for ART in the 12 months post-HIV index date, one or more hospitalization post-HIV index date and one or more emergency department visit post-HIV index date.

**Statistical methods**

The cumulative prevalence was reported with a two-sided 95% CI calculated using the large sample normal approximation. Descriptive statistics were used to report demographics, clinical characteristics, and ART information. Means and standard deviations (SDs) were reported for continuous variables, and frequencies and percentages were reported for categorical variables. Statistical significance between cohorts was assessed using the chi-square test for categorical variables or the \(t\)-test for continuous variables to identify covariates associated with meeting the definition of HIVAW for use in multivariable modeling. Multivariable logistic regression analyses were conducted to assess demographic and clinical correlates of HIVAW with odds ratios and 95% CIs presented. The analyses were conducted using SAS version 9.4 (Cary, North Carolina, USA).

**Results**

A total of 42,587 PWH were identified over the 2012–2018 study period (Table 1). From the PWH study population, 7804 met the definition of HIVAW (Table 1). The estimated HIVAW cumulative prevalence between July 2012 and March 2019 was 18.3% (95% CI 18.0–18.7%). Estimated annual prevalence was 2.7% per year (18.3/6.75-year study period). Among those with a claim for ART during the 12 months post-HIV index date \((n = 27,223, 63.9\% \text{ of the total PWH study population})\), the cumulative prevalence of HIVAW was 17.9% (95% CI 17.4–18.3%; \(n = 4,871\)) during the study period. Among those without a claim for ART during the 12 months post-HIV index date \((n = 15,364; 36.1\% \text{ of total})\) the cumulative prevalence of HIVAW was 19.1% (95% CI 18.5–19.7%; \(n = 2,933\)). Evaluating prevalence by insurance type, HIVAW cumulative prevalence was 23.5% (95% CI 23.0–24.0%; \(n = 6,764/28,741\)) in the Medicaid population and 7.5% (95% CI 7.1–8.0%; \(n = 1,040/13,846\)) in the Commercial and Medicare Supplemental population.

**Baseline characteristics**

The study population was predominantly male (61.7% in the HIVAW cohort and 65.3% in the non-HIVAW cohort, \(P < 0.0001\); see Table, Supplemental Digital Content 1, http://links.lww.com/QAD/C334). The HIVAW cohort were more likely to be older with a mean age of 46.4 (12.0 SD) years vs. 43.5 (12.5 SD) years for the non-HIVAW cohort (unadjusted \(P < 0.0001\)). Additionally, a higher percentage of the HIVAW cohort were on Medicaid compared with those in the non-HIVAW cohort (86.7% vs. 63.8%, unadjusted \(P < 0.0001\)). In the Medicaid population, nearly three-fourths of patients in the HIVAW and non-HIVAW cohorts were Black. Within the Commercial and Medicare Supplemental population, there were no significant differences in geographic distribution between cohorts, and over half of patients in the HIVAW and non-HIVAW cohorts had a Preferred Provider Organization insurance plan. There was no difference in percentage of PWH with two or more claims for CD4\(^+\) cell count or viral load tests.

**Selected HIV/AIDS opportunistic infections and comorbidities**

The most common opportunistic infections in the HIVAW cohort were severe candidiasis (13.1%), herpes zoster (10.7%), severe herpes simplex (6.8%), and \textit{Pneumocystis carinii jirovecii} (5.5%) (see Table, Supplemental Digital Content 2, http://links.lww.com/QAD/C334). The proportion with one or more diagnosis claim of an opportunistic infection or HIV/AIDS-related condition was 64.2% in the HIVAW cohort and 38.6% in the non-HIVA cohort (unadjusted \(P < 0.0001\); see Table, Supplemental Digital Content 2, http://links.lww.com/QAD/C334).
Comorbidity burden in the HIVAW and non-HIVAW cohorts are shown in Fig. 2a (CCI) and Fig. 2b (other comorbidities). The metabolic disorders were frequent in the HIVAW cohort with lipodystrophy (37.5%) and dyslipidemia (48.5%) (Fig. 2b). Over 40% of the HIVAW cohort had psychiatric medical claims including various disorders of anxiety, depression, and substance use and addiction (Fig. 2b). The most common substance use and addiction disorders were cannabis-, tobacco-, and opioid-related disorders. There were no documented claims for stimulant-related disorders including methamphetamine use (see Table, Supplemental Digital Content 2, http://links.lww.com/QAD/C334).

The mean CCI score in the HIVAW cohort was 3.6 (3.0 SD) compared with 2.0 (2.2 SD) in the non-HIVAW cohort (see Table, Supplemental Digital Content 3, http://links.lww.com/QAD/C334). These CCI scores were influenced by differences in pulmonary disease (45.1 vs. 26.2%), diabetes (28.1 vs. 20.0% without chronic complications; 11.7 vs. 6.8% with chronic complications), renal disease (24.1 vs. 11.0%), cerebrovascular disease (21.2 vs. 8.9%) and heart
failure (18.7 vs. 7.1%) (see Fig. 2a, Table, Supplemental Digital Content 3, http://links.lww.com/QAD/C334).

Antiretroviral therapy utilization
Over 35% of PWH had no evidence of ART claims in the 12 months post-HIV index date; this proportion was higher in the Medicaid population than in the Commercial and Medicare Supplemental population (44.3%; n = 12 729/28 741 vs. 19.0%; n = 2635/13 846). For those with an ART claim, cART was the most commonly prescribed treatment within the Medicaid population (60.1%; n = 9624/16 012), whereas STR was the most common in the Commercial and Medicare Supplemental population (72.6%; n = 8144/11 211) (Fig. 3). The proportions of patients with ART claims were similar (yet statistically significant) in the HIVAW and non–HIVAW cohorts (62.4 and 64.3%, unadjusted P < 0.0001; see Table, Supplemental Digital Content 1, http://links.lww.com/QAD/C334).

Correlates of HIV-associated wasting
The original logistic regression model was planned to include only main effects; however, due to the difference in ART prescription claims observed by insurance type (Fig. 3), an interaction between ART and insurance type was included in the model. After adjustment (Fig. 4), the strongest associations with HIVAW were having Medicaid insurance and post-HIV index date hospitalization(s). Other factors associated with HIVAW were older age; being male; having more comorbidities; presence of ≥1 diagnoses of opportunistic infections or HIV/AIDS-related conditions; claims for two or more CD4+ cell count and/or viral load tests 9 months pre or post-index; and emergency department visit(s). Black race and ART use were not found to be correlated with HIVAW in the model.

Discussion
The management of HIV infection, especially with advances in ART, has progressed over the decades, allowing PWH to live longer and with lower rates of morbidity. HIV infection is considered a chronic, manageable disease. However, HIVAW continues to exist in PWH. Medical literature cites that the cause of HIVAW is multifactorial and cannot be completely addressed by ART or maintaining viral control [13–15].

An analysis of a large US managed care claims database involving 75 health plans of approximately 51 million patient lives demonstrated that 7–8% of patients diagnosed with HIV/AIDS had a concomitant diagnosis of, or treatment for, HIVAW or cachexia cumulatively from 2004 to 2005 [16]. This was followed by the healthcare claims database study by Siddiqui et al. [9] (2005–2007), which estimated the prevalence and burden of HIVAW in commercially insured PWH with evidence of HIV infection. The authors reported a cumulative prevalence of 8.3% (over a 2.5-year period, approximately 3.3% annually) in commercially insured PWH who had evidence of HIVAW (defined as weight loss–associated conditions, anorexia symptoms, treatments for weight loss or wasting). Additionally, Tang et al. [17] observed that the prevalence of HIVAW was higher in males compared with females. These past studies demonstrated the ongoing occurrence of HIVAW.

The present study was conducted to understand HIVAW prevalence across US payer markets in the era of modern ART over the years 2012–2018. Given that HIVAW does not have a unique ICD-9-CM or ICD-10-CM code, PWH with evidence of HIVAW were identified by proxy, based on the algorithm described by Siddiqui et al. [9].
Our study found that over approximately 6 years, 18.3% of PWH receiving medical care met the definition of HIVAW (approximately 3.1% annually). These findings are similar to the previous studies, demonstrating an average annual prevalence of approximately 3%. Among PWH with Medicaid coverage, the cumulative prevalence of HIVAW rose to 23.5% of PWH over 6 years (approximately 3.9% annually).

Results demonstrated that modern ART was not correlated with HIVAW. The proportions of patients with HIVAW did not differ between those with ART claims in the 12 months post-HIV index date compared with those without ART claims (17.9% vs. 19.1%; respectively, adjusted \( P = 0.2628 \)). This observation confirms previous evidence that HIVAW continues to occur in PWH who receive ART [9,18–20]. In our study, more than 35% of PWH in both cohorts had no evidence of ART claims in the 12 months post-HIV index date, which is consistent with previously published prescription use data [21]. This allowed the authors to evaluate the association between HIVAW prevalence and ART use. The authors found HIVAW was most strongly associated with having Medicaid coverage and post-HIV index date hospitalization(s), and not ART use.

The previous HIVAW cumulative prevalence estimate of 8.3% from 2005 to 2007 was based on a medical and pharmacy claims analysis of a commercial PWH population [9]. Of note, the first STR was approved in 2006 and the next one in 2011 [22]. Therefore, Siddiqui et al.’s study [9] was prior to STRs being widely available, which is why further study was needed. Additionally, the authors reported that PWH with HIVAW were more likely to have evidence of ART (90.0%) compared with non-HIVAW (80.7%) during the study period, whereas in the present study, these groups had similar ART utilization rates. The proportions of PWH with comorbid conditions, opportunistic infections and selected HIV/AIDS conditions were higher in our study compared with Siddiqui et al. [9]; however, both studies demonstrated an overall increased comorbidity burden in the HIVAW cohorts. As PWH are living longer, they remain at a higher risk of age-associated comorbidities including HIVAW [1,3]. Although it is unclear how to describe the association between HIVAW and other comorbidities (causal, which came first, can one predict the other, etc.), the fact that these associations are present across almost all comorbidities warrants additional studies of HIVAW etiology.

Finally, our study provided a better understanding of the Medicaid population, which had not been evaluated previously because the evolution of electronic Medicaid databases in the US was in its infancy. Medicaid is the largest source of insurance coverage for PWH [23]. The findings from our study suggest that HIVAW was disproportionately represented among those who have Medicaid coverage compared with other insurance types. The observations from our study suggest the need for additional research to further understand the differences in prevalence rates of HIVAW based on payer types.

**Limitations**

In the United States, claims databases allow for analysis of large numbers of patients over time and may be generally representative of the US patient population, especially when including the Commercial, Medicare Supplemental and Medicaid populations [24]. However, claims data are collected for reimbursement purposes and not specifically for research, and the lack of clinical variables limit the inferences that can be made from such data.

As there is no ICD code specifically for HIVAW, a proxy definition based on weight loss–related codes and treatments was used in the algorithm. These algorithms...
included appetite stimulants, non-testosterone anabolic agents, and enteral and parenteral nutrition which may be used for other non-HIVAW conditions; therefore, the prevalence of HIVAW might be overestimated. A sensitivity assessment including only patients with claims for a wasting-associated condition (Criteria A in Table 1) estimates the cumulative prevalence of HIVAW is 16.1% over 6 years as a lower boundary. The algorithm used to identify HIVAW, based on Siddiqui et al. [9] was developed by clinical and coding experts; however, validation studies are needed.

This database study evaluated a prevalent population as the onset of HIVAW was unknown. Accordingly, the temporal relationship between ART use, ART classes, or opportunistic infections and HIVAW cannot be determined. Furthermore, ART status was based on presence of claims in a 12-month period post-HIV index date and may not have coincided with claims for the HIVAW definition used.

The majority of patients included in the study were on Medicaid insurance; historically, these patients have lower education and income levels, more disability, and less access to transportation and stable housing compared with non-Medicaid patients [25–27]. These demographic factors were not available for evaluation, but their possible presence could contribute to a higher prevalence of HIVAW. Substance use was higher in the HIVAW cohort. However, there were no claims for stimulant-related disorders, including methamphetamine; therefore, it was likely that substance use is being under-reported and/or under-coded in both cohorts.

We found evidence of HIVAW among PWH regardless of HIVAW etiology. We believe that the original algorithm as presented by Siddiqui et al. [9], as well as the modified algorithm in this study, continue to establish a basis upon which further HIVAW studies can be elucidated.

Conclusion
HIVAW increases morbidity and mortality [4,5] but has received little attention, including prospective clinical research, in the era of modern ART. This medical and pharmacy claims database study demonstrated that, over approximately 6 years, 18.3% of PWH with insurance coverage met the definition for HIVAW. Additionally, a subset of patients with Medicaid insurance coverage or those with a history of hospitalization were found to have an even higher prevalence of HIVAW. These data suggest the need to monitor for unintentional weight loss in PWH, understand the complex and multifactorial etiologies of HIVAW, and evaluate the risk of HIVAW by comorbidities and payer type. As the population of PWH continues to age, the risk of developing frailty (which includes weight loss) will be another important health assessment for this vulnerable population.

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Conflicts of interest
J.S. has received consulting and speaking fees from AbbVie; BioFire; Cumberland; EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA; and Merck Sharp & Dohme. S.K.S., B.H., K.A.W., A.P. and M.H. are employees of EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA. K.L.D. and Q.H. are employees of EPI-Q, Inc., which received payment from EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, for the development and execution of this study.

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