Per-partner condom effectiveness against HIV for men who have sex with men

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Objective: Few studies have examined condom effectiveness for HIV prevention among MSM. We estimated condom effectiveness per partner in four cohorts of MSM during 1993–2003 (JumpStart, Vaccine Preparedness Study, VAX004 and Project Explore).

Methods: We used logistic regression to estimate the increase in odds of new HIV infection per HIV-positive partner for condom-protected receptive anal intercourse (PRAI; partners with whom condoms were always used) and condomless (unprotected) receptive anal intercourse (URAI; partners with whom condoms were sometimes or never used). To estimate condom effectiveness for preventing HIV transmission, we applied the concept of excess odds, the odds ratio minus 1. The condom failure rate was estimated as the excess odds per PRAI partner divided by the excess odds per URAI partner. Condom effectiveness was then 1 minus the failure rate.

Results: The excess odds of HIV infection per HIV-positive partner were 83% for URAI and 7% for PRAI. The resulting failure rate (9%) indicated per-partner condom effectiveness of 91% (95% confidence interval 69–101).

Conclusion: The increase in odds of new HIV infection per HIV-positive partner for receptive anal intercourse was reduced by 91% for each partner with whom condoms were always used.

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Introduction

Among MSM, number of partners for unprotected (condomless) receptive anal intercourse (URAI) has long been recognized as a risk factor for HIV infection. Before the cause of AIDS was known, a national case-control study identified number of male sex partners in the preceding year as the variable most closely associated with Pneumocystis and Kaposi sarcoma among gay and bisexual men [1]. Soon after HIV testing became available, it was shown that the most important risk factor for seroconversion was the number of URAI partners (29% with no recent partners to 85% with $\geq$3 partners) [2]. Another study found that HIV infections increased 9.5% per partner during the preceding 30 months [3].

Although HIV transmission risks have been reported [4,5], only recently have quantitative condom effectiveness studies been conducted for MSM. Early studies defined condom failure in terms of reported slippage and breakage, without regard to whether infection occurred [6,7]. Meta-analyses of condom effectiveness among heterosexual populations have reported widely ranging estimates of 69% [8], 90–95% [9], and 80% [10] that varied according to analytical methods. A 2014 systematic review found no eligible estimates of condom effectiveness for anal sex and substituted the 80% estimate for vaginal sex to estimate the risk of transmission through condom-protected receptive anal intercourse (PRAI) [11].

In 2014, Scott *et al.* [12] used data from four large MSM cohorts to estimate transmission risk per act of PRAI (0.04–0.08%) and URAI (0.60–0.73%) with HIV-positive partners, but did not directly examine condom effectiveness. In 2015, Smith *et al.* [13] used two of the

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same four data sets to estimate condom effectiveness per act of receptive anal intercourse (RAI) with HIV-positive partners (63%), as well as per person-year (72%) without regard to number of acts or partners.

Condom effectiveness can be estimated by comparing the risk, odds, or hazard of HIV transmission when condoms are used vs. when they are not used, with exposure quantified per act, per partner, or per person-time. Some analyses have compared person-time infection rates between those who use condoms always vs. never, regardless of number of acts or partners [10,13]. Others have estimated the per-act risk of infection with and without condoms, which permits estimating condom effectiveness for a single occasion of receptive sex [12,13]. However, for MSM, by far the most commonly reported unit of exposure for transmission risk has been by partner: a meta-analysis including 13 studies of MSM found 11 studies that measured URAI risk per partner but only two that measured URAI risk per act [4]; PRAI risk, and therefore, condom effectiveness were not examined.

Because of the variance in viral load among HIV-positive partners, the number of URAI partners may be more closely related to accumulated risk (and thus, to condom effectiveness) than is the number of occasions or person-years [14–17]. A per-partner estimate of condom effectiveness may be useful for modeling studies as well as in developing and updating tools that help people estimate their risk for HIV infection (see the Centers for Disease Control and Prevention's HIV Risk Reduction Tool at https://wwwn.cdc.gov/hivrisk/). Thus, we sought a per-partner estimate of condom effectiveness. We applied logistic regression to data from four cohorts of MSM [18–23] to examine the association between newly acquired HIV infection and number of HIV-positive partners with whom condoms were used always vs. less than always during RAI. We then compared the odds of infection with and without condoms to estimate per-partner condom effectiveness for MSM. Finally, we compared our estimates with results from previous analyses.

Methods

For the current analyses, data were combined from four prospective longitudinal HIV prevention studies: the CDC Collaborative HIV Seroincidence Study (JumpStart, 1993–1994) [18], the HIVNET Vaccine Preparedness Study (VPS, 1995–1997) [19], the rpg120 Vaccine Study (VAX004, 1998–2002) [20–22], and Project Explore (1999–2003) [23]. The four studies shared several key characteristics that facilitated combined analysis. Each study tested and enrolled HIV-negative MSM who reported anal intercourse with at least one male partner in the preceding 12 months. Every 6 months, participants were tested for HIV and interviewed concerning sexual behavior up to a specified duration or until infection. The intended duration for each study was at least 18 months (36 months for VAX004, and 48 months for Project Explore). Some studies included women, as well as men who did not have sex with men, but they were excluded from these analyses.

Sexual risk behavior data were collected in all four studies via self-report, and included numbers of occasions and partners, by serostatus, for insertive or receptive oral or anal sex with and without condoms during the preceding 6 months. Specifically, participants in each study were first asked the number of men they had oral or anal sex with, by perceived serostatus (HIV-positive, HIV-negative, or unknown). For each serostatus, they were then asked the number of occasions of five sexual activities: URAI, PRAI, insertive anal sex with and without condoms, and receptive oral sex to ejaculation without condoms.

In all four studies, HIV status of participants was based on clinical results of HIV testing by the standard procedures of the time (enzyme-linked immunosorbent assay followed by either a western blot or immunofluorescence assay) conducted by study staff; HIV-positive status of partners was based on the study participant's perception.

Procedures

To examine condom effectiveness under the highest risk circumstances, we chose number of HIV-positive RAI partners as the unit of exposure [17]. For analysis, we selected data from the final study visit for which the necessary behavioral data and HIV test results were available. For participants who became infected with HIV during the study, the final study visit was the first visit where they received a positive test result, at which point they no longer continued in the study. We then retained only those participants who reported, during their final visit, at least one HIV-positive male sex partner during the past 6 months, whether for oral or anal sex, as insertive or receptive partner, and with or without condoms.

We then created two variables for RAI: number of HIV-positive partners with whom, during the preceding 6 months, condoms were always used when the study participant was the receptive partner (PRAI) and number with whom condoms were sometimes/never used when the study participant was the receptive partner (URAI). Participants who reported no RAI with HIV-positive partners during the interval were coded as having zero HIV-positive partners for both URAI and PRAI, indicating that their sexual activity with HIV-positive partners (an inclusion criterion for this analysis) was limited to oral or insertive anal sex. For about 5% of participants, the data did not allow precise calculation of the two variables of interest; this tended to occur when the number of partners was large. In this case, we allocated

the number of partners to sexual activities in proportion to the number of acts reported.

Logistic regression was performed for the data from each study and for the pooled data set. The dichotomous outcome was new HIV infection, with two count-level predictor variables: numbers of HIV-positive partners for URAI and for PRAI in the past 6 months. From this model, the condom failure rate can be estimated by the relative excess odds [24] (see Appendix for details, http://links.lww.com/QAD/B269):

$$per\ partner\ condom\ failure\ rate = \frac{OR_{PRAI} - 1}{OR_{URAI} - 1}$$

Per-partner condom effectiveness is then 1 − the failure rate [9].

We applied a bootstrap procedure to obtain 95% confidence intervals for the point estimate of effectiveness [25]. Statistical heterogeneity of condom effectiveness among the four studies was tested by the Q statistic, which is distributed as chi square with, in this instance, three degrees of freedom (four studies except one).

From all analyses, we excluded one response from the VAX004 study which was an influential observation, defined as a participant whose inclusion or exclusion leads to a large difference in results [26]. This exclusion was the conservative option because removal of this response decreased the estimate of condom effectiveness for that study. Residual analyses indicated that removal of the next three most influential observations would have increased our estimates of condom effectiveness.

Results

The sample of men who reported oral or anal sex with an HIV-positive male partner during the 6 months before their final study visit constituted 3262 participants. Of these, 335 were from JumpStart (10%), 605 from VPS (19%), 1540 from VAX004 (47%), and 782 from Project Explore (24%). Most (2712) were non-Hispanic white (83%); 262 were Hispanic/Latino (8%), 140 non-Hispanic African American (4%), and 148 Asian or other race or ethnicity (4%). Nearly a third (987; 30%) were ages 18–30, 775 (24%) were ages 31–35, and 1500 (46%) were age 36 or older. One-fifth (658; 20%) had a high school degree or less, 1741 (53%) had a college degree or some college, and 862 (26%) had a graduate or professional degree or some training beyond a bachelor's degree. Data were collected from 1993 through 2003.

In the overall sample of 3262 men who had sex with HIV-positive men, 1828 (56%) reported no RAI with these partners (that is, only oral or insertive anal sex). Among those who did have RAI, the HIV-positive partners of 871/1434 (61%) always used condoms with them (PRAI), constituting 871/3262 (27%) of the study sample. Thus, 563/3262 (17%) of the sample reported URAI with HIV-positive partners in the preceding 6 months.

At their final visit, 289/3262 (8.9%) participants tested HIV-positive, ranging from 4.8% in VPS to 12.5% in Project Explore. Among 1828 participants who reported no RAI with HIV-positive partners, 66 (3.6%) acquired HIV infection. Among 871 participants who reported PRAI but no URAI with HIV-positive partners, 79 (9.1%) acquired HIV infection. Among 563 participants who reported URAI with HIV-positive partners, 144 (25.6%) acquired HIV infection.

HIV infection and number of HIV-positive partners for receptive anal intercourse with and without condoms

Across the four studies, odds ratios per HIV-positive partner for URAI ranged from 1.40 to 3.48, reflecting an increase in odds of acquiring HIV infection ranging from 40 to 248% per partner (Table 1). In the pooled analysis, the overall odds ratio (1.83) indicates an increase in odds of new HIV infection of 83% per URAI partner [95% confidence interval (CI) 59–111]. Odds ratios per partner for RAI with whom condoms were always used (PRAI) ranged from 1.01 to 1.11, indicating a 1–11% increase in odds, with a pooled odds ratio of 1.07, thus a 7% increase (95% CI 1% decrease to 16% increase). According to the model, the proportion who acquired HIV infection

Table 1. Odds ratios for condom-protected receptive anal intercourse (PRAI) and unprotected (condomless) receptive anal intercourse (URAI), failure rate, and effectiveness of condom use to reduce HIV acquisition among MSM; four studies separately and combined, 1993–2003.

	Odds ratio (95% CI)			Condom effectiveness percentage	
Study	PRAI	URAI	Condom failure rate (%)[a]	Point estimate [b] (95% CI)	Median (IQR)
All four	1.07 (0.99–1.16)	1.83 (1.59–2.11)	8.8 (0.07/0.83)	91.2 (69.0–101.1)	90.7 (86.3–94.2)
JumpStart	1.04 (0.67–1.60)	1.69 (1.05–2.73)	5.2 (0.04/0.69)	94.8 (−107.5 to 164.5)	95.0 (74.8–116.2)
VPS	1.01 (0.74–1.36)	2.64 (1.47–4.75)	0.4 (0.01/1.64)	99.6 (67.2–124.3)	99.0 (95.4–103.2)
VAX004	1.11 (0.98–1.25)	1.40 (1.20–1.63)	26.9 (0.11/0.40)	73.1 (−88.7 to 98.7)	71.4 (45.5–84.3)
Explore	1.11 (0.90–1.37)	3.48 (2.50–4.84)	4.5 (0.11/2.48)	95.5 (82.8–104.5)	95.9 (92.8–98.5)

[a]Failure rate is estimated by the ratio of excess odds as shown, where excess odds = odds ratio − 1.
[b]Point estimate of condom effectiveness is 1 − failure rate for the model where each observation is sampled with probability = 1. The 95% confidence interval (CI), median, and interquartile range (IQR) were obtained from bootstrap procedure.

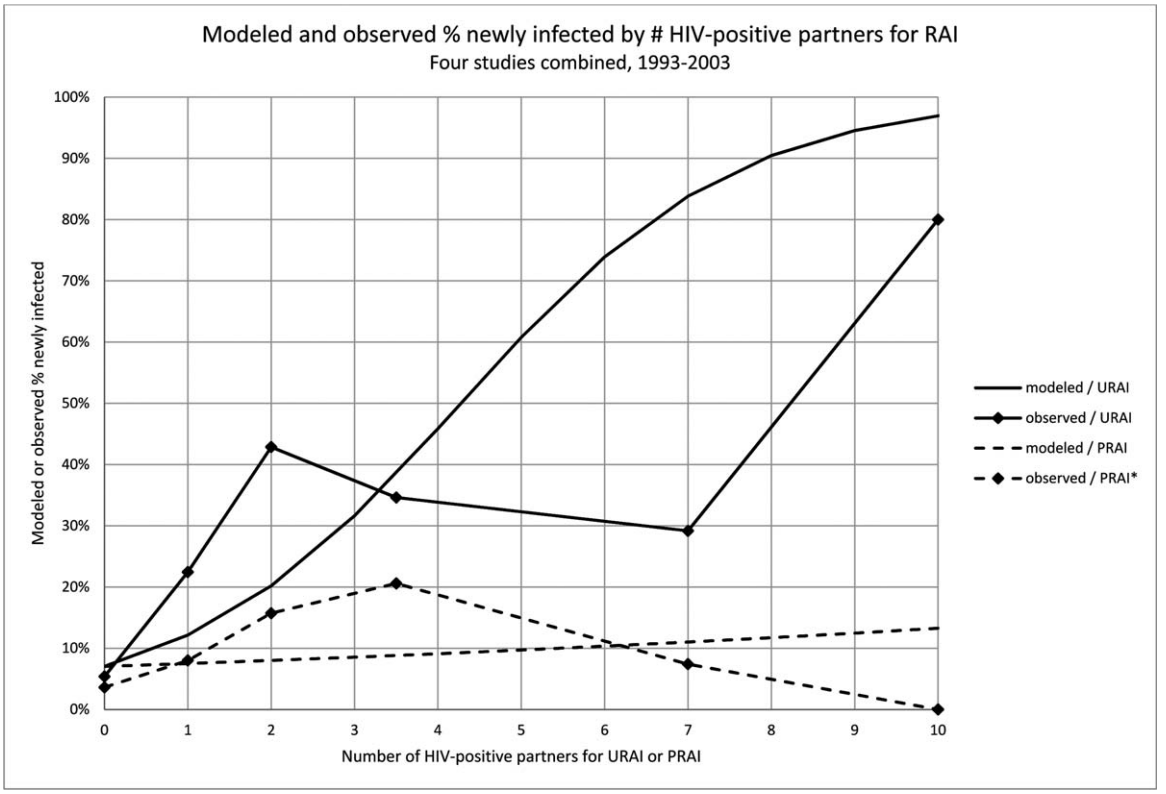

Fig. 1. Modeled percentage newly infected, by number of HIV-positive partners for condom-protected and unprotected receptive anal intercourse (PRAI and URAI) in preceding 6 months. Four studies combined, 1993–2003, $N = 3262$. Observed newly infected/total by number of URAI partners: 145/2699 (0 partners), 103/459 (1), 21/49 (2), 9/26 (3–4), 7/24 (5–9), 4/5 (10+). Total N for this observed series = 3262, including all participants. *Observed newly infected/total by number of PRAI partners: 66/1828 (0 partners), 59/737 (1), 11/70 (2), 7/34 (3–4), 2/27 (5–9), 0/3 (10+). Total N for this observed series = 2699 including only participants who reported no URAI, to more specifically illustrate risk associated with PRAI only.

increased rapidly with number of HIV-positive partners for URAI, but not for PRAI (Fig. 1); the categorized raw percentage positive is also shown for comparison.

Condom failure and effectiveness

The condom failure rates from the four studies ranged from 0.4 to 27% (pooled failure rate, 9%); thus condom effectiveness ranged from 73 to 99.6% (pooled effectiveness, 91%; 95% CI 69–101; Table 1). The four separate estimates were statistically homogeneous (Q for heterogeneity with 3 d.f. = 0.3, $P = 0.96$), indicating that it is reasonable to combine results across the four studies.

Comparison with previous analyses

Scott *et al.* [12] used the same four data sets we used but estimated the risk per act of PRAI and URAI (Table 2). The estimated risk per act of PRAI with HIV-positive partners was 0.04% for JumpStart and 0.08% for the other three studies pooled; per act of URAI with HIV-positive partners, the risk was 0.60% (JumpStart) and 0.73% (pooled studies). Although the ratios of these values were not presented in the article, a point estimate for condom effectiveness per act of RAI can be calculated from the reported data as 1 − the failure rate, or $1 - 0.04/0.60 = 93\%$ for JumpStart and $1 - 0.08/0.73 = 89\%$ in the other three studies; confidence intervals were not available.

Smith *et al.* [13] applied two analytical methods to two of the same four data sets. The pooled estimate of risk per act (both studies) was 0.20% for PRAI and 0.54% for URAI. The ratio comparing these two per-act risks was $(0.20/0.54) = 37\%$, for a condom effectiveness estimate of 63% (95% CI 47–74). However, this pooled estimate was composed of very different results from the two studies: condom effectiveness was estimated as 46% per act in VAX004, compared with 87% in Project Explore, with nonoverlapping confidence intervals (Table 2).

In terms of condom effectiveness per person-year in Smith *et al.* [13], the pooled hazard of infection was 3.8% per person-year among those reporting always using condoms with HIV-positive partners for RAI vs. 13.2% per person-year for those never using condoms with HIV-positive partners for RAI. The reduction in infection rates per year (regardless of number of acts or partners) was 72% (95% CI 61–81) pooling the two studies, again composed of rather different study-specific

Table 2. Modeled point estimates of increase in percentage newly HIV-seropositive associated with condom-protected and unprotected receptive anal intercourse (PRAI and URAI) among MSM with HIV-positive partners, and condom effectiveness according to different analytical methods, measures, and data sets, 1993–2003.

Reference	Metric and unit of exposure	Data sets	Increase in risk, hazard, or odds of new HIV infection per unit		Condom effectiveness (95% CI)
			PRAI	URAI	
Scott *et al.* [12]	Risk per act	J	0.04%	0.60%	93%[a]
		P V E	0.08%	0.73%	89%[a]
Smith *et al.* [13]	Risk per act	V E	**0.20%**	**0.54%**	**63% (47–74)**
		V	0.22%	0.41%	46% (19–64)
		E	0.15%	1.11%	87% (73–94)
	Hazard per person-year	V E	**3.8%**	**13.2%**	**72% (61–81)**
		V	4.4%	11.9%	64% (45–76)
		E	2.2%	16.1%	87% (73–94)
This analysis	Odds per partner	J P V E	**7.3%**	**83%**	**91% (69–101)**
		P V E	7.5%	84%	91% (68–101)
		V E	9.5%	75%	87% (47–99)
		J	3.6%	69%	95% (−107–164)
		P	0.7%	164%	100% (67–124)
		V	10.8%	40%	73% (−89–99)
		E	11.1%	248%	96% (83–104)

CI, confidence interval; J, JumpStart; P, Vaccine Preparedness Study; V, VAX004; E, Project Explore. Bold text indicates summary estimates in analyses that aggregated across multiple data sets.
[a]These two condom effectiveness estimates were not presented in the published article; we calculated them from the published risk per act for PRAI and URAI. Confidence intervals were not available.

estimates: 64% for VAX004 and 87% for Project Explore. Our corresponding estimates are shown for comparison for each study and combination.

Discussion

On average, consistent condom use for RAI with an HIV-positive partner reduced the odds of acquiring HIV from that partner by 91%. This estimate reflects the difference between an 83% increase in odds of new HIV infection for each HIV-positive partner with whom RAI was sometimes or never condom-protected vs. an increase of only 7% for each HIV-positive partner with whom RAI was reported as always condom-protected.

Approaching 40 years of the HIV epidemic, little information has been available concerning condom effectiveness for MSM, the population at the greatest risk for infection in the United States. Because of heterogeneous numbers of partners and acts, ostensible degrees of risk based on relative frequency of condom use (always, sometimes, or never) do not consistently reflect increasing degrees of exposure [27–30]. This new result based on number of partners for unprotected sex suggests the need for more specific health messages that promote incremental risk reduction.

Our estimates of per-partner condom effectiveness were similar to per-act estimates that we derived from Scott *et al.* [12]. However, our estimates were greater than the per-act and per-person-year estimates reported by Smith *et al.* [13]. The greater effectiveness observed here may be because of including two additional data sets and the focus on partner-level analyses vs. act or person-year. Also, the three estimates of condom effectiveness specific to VAX004 (46% per act and 64% per person-year from Smith *et al.* [13], and 73% per partner from our analysis) were lower than any estimates for the other three studies (87%–100%), in some cases statistically significantly so.

Whether effectiveness is estimated per act as in Scott *et al.* [12] and Smith *et al.* [13], in time to event as in Smith *et al.* [13], or per partner as in our analysis, all models involve simplifying assumptions. Refinements could be applied to count the number of occasions of PRAI and URAI with each partner, but such data are not usually available, and prevention messages based on such an analysis could be unduly complex. Furthermore, it is not clear that the results would be informative: an early study found that after accounting for number of partners, the number of occasions of anal sex with HIV-positive partners was significantly negatively associated with infection [3]. This result could occur if some participants acquire HIV after only a few occasions with a highly infectious partner, whereas others remain uninfected after many occasions, perhaps because the partner has a low viral load. A study of heterosexual HIV-discordant couples found that 'the Bernoulli process model of HIV transmission is acceptable on a per-partner basis, but not on a per sex act basis' possibly because of a 'different per sex act infectivity for each infected member of the population' [31]. A more recent meta-analysis of mostly MSM studies found that 'empirical per-partner study estimates do not show the expected increase in infectivity with increasing number of sexual exposures to the index partner ... implying that

the assumption of independence of risk per act within a partnership is invalid' [4].

Our finding that only 17.3% of this sample had URAI with HIV-positive partners in the past 6 months may seem to contrast with a previous report that only 16.4% always used condoms with all partners for both insertive and receptive sex during all study periods for up to 4 years [13]. This difference serves as a reminder that findings can vary greatly by time frames, behaviors, and partner types (e.g. serostatus, main vs. casual).

Limitations

The logistic model we used does not explicitly account for infection through oral sex or insertive anal sex with HIV-positive partners, from any type of sexual activity with partners of unknown HIV status or partners incorrectly perceived as HIV-negative, or from unreported sexual behavior, nor for potential cofactors such as other sexually transmitted infections or drug use [32–34]. Preliminary analyses including these variables indicate that the present results are robust to inclusion of such additional variables (manuscript in preparation). Some analyses have examined risk or condom effectiveness with insertive as well as receptive sex [12,13]. We analyzed only receptive sex because epidemiology indicates that receptive sex poses the greater risk [1,2,4].

The data sets were limited in several ways. They were not very diverse ethnically, and detailed partner characteristics such as viral load were not available. Also the timespan of these four studies (1993–2003) predates the widespread availability of the most effective antiretroviral therapies for persons with HIV, as well as the advent of preexposure prophylaxis (PrEP). Nevertheless, these longitudinal seroconversion studies are among the largest available sources of such data on sexually active MSM and provide an optimal design for this analysis.

The comparative merits of measuring exposure per partner, per act, and per year are not addressed in our analysis and remain an empirical question. Although we have summarized results from other studies using somewhat different methods, future research could use relative excess odds to directly compare the results across different units of exposure.

Conclusion

Our analyses support the continued promotion of condoms as an effective strategy for preventing HIV infection. Further research is needed to explore the association between HIV acquisition and measures of sexual risk (e.g. number of partners, number of unprotected acts, serosorting, seropositioning) as well as other perceived partner HIV statuses (i.e. negative and unknown) and to examine associated condom effectiveness estimates. Researchers should consider including appropriate survey questions to further address these issues in studies that measure rates of new infection. Even if the number of new infections is low in any one study, meta-analysis can provide useful summary effects and associations across studies. Quantifying these relationships can inform HIV prevention messaging, mathematical modeling, and other HIV prevention planning activities.

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Conflicts of interest

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Authors' contributions: Wayne Johnson contributed to all aspects of the manuscript, including literature search, figures, study design, data collection, data analysis, data interpretation, and writing. Ann O'Leary and Steve Flores contributed to study design, data analysis, data interpretation, and writing. All three authors meet all four ICMJE criteria for authorship.

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