A Systematic Review of the Inclusion (or Exclusion) of Women in HIV Research: From Clinical Studies of Antiretrovirals and Vaccines to Cure Strategies

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Introduction: The effect of clinical interventions can differ because of sex/gender. Studies have shown that women are often under-represented in medical research. The aim of this systematic literature review was to characterize women's participation in HIV clinical studies of antiretroviral drugs (ARV), prophylactic vaccines (VAX), and curative strategies (CURE).

Methods: Systematic PubMed searches were conducted to identify ARV, VAX, and CURE studies. Data were extracted on the number of women, date of publication, sources of funding, country of study, and trial phase. Correlates of female participation were assessed.

Results: Women represented a median of 19.2% participants in ARV studies (387), 38.1% in VAX studies (53), and 11.1% in CURE studies (104). Funding source was not correlated with the proportion of female participants in VAX and CURE studies but was for ARV studies (P = 0.03). ARV trials funded by private noncommercial sources had the highest proportion of women, whereas publicly funded trials had the lowest female participation (median 16.7%). The median proportion of women in ARV trials that were fully or partially funded by the National Institutes of Health was significantly lower than the median in trials funded by other sources (19.6% vs. 22.3%, P = 0.001).

Conclusions: Although women comprise nearly half of people living with HIV, they continue to be under-represented in clinical studies. Despite federal policies that have been established to address this, our study shows that publicly funded ARV trials recruit even fewer women than other trials. There is an urgent need to ensure that HIV clinical studies consider sex/gender dimensions.

Key Words: clinical trials, sex, gender, HIV, vaccines, antiretroviral drugs, curative strategies, eradication

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INTRODUCTION

Sex and gender differences in prevalence, incidence, symptomatology, progression, or outcome have been noted across a range of diseases.[1–4] Differences in pharmacokinetics (PK) and pharmacodynamics, such as body surface, hepatic function, drug metabolism, absorption, and clearance, can result in different treatment responses.[5–7] In addition, sex and gender differences related to economic power, health literacy, and life experience, can influence health-seeking behavior and access to and utilization of healthcare services by women, men, and transgender persons.[8–10]

In HIV infection, sex and gender dynamics affect risk of acquisition, rate of disease progression and access, and response to antiretroviral treatment. For example, women are at higher risk of penile-vaginal HIV transmission than men because of biological and social factors.[11] Furthermore, although women have higher CD4 counts and lower viral loads at the onset of disease[12] but faster disease progression than men at the same viral loads,[13–15] men show a slower CD4 recovery and higher mortality rates even when corrected for viral suppression.[16] Likely attributable to differences in PK and pharmacodynamics, differential adverse event profiles have been observed between men and women. For instance, women are at increased risk for rash, lactic acidosis, pancreatitis, and fat accumulation,[17] which may in part explain observed sex differences in treatment adherence.[18]

Historically, women of childbearing age have been excluded from clinical research because of concerns for potential harm to the fetus and also to minimize variations in study results introduced by hormonal cycles,[19] leading to a dearth of data to systematically analyze sex/gender differences.[20] In 1993, the US Congress passed the *National Institutes of Health (NIH) Revitalization Act* (PL 103-43),[21]

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which requires NIH to ensure inclusion of women in clinical research by mandating that any clinical trial funded by NIH is designed to allow for meaningful sex- and gender-based analyses. In the same year, the Food and Drug Administration (FDA) withdrew the restriction on participation of women of childbearing potential from early clinical trials and issued guidance regarding the inclusion of all sexes in drug development studies, analysis of clinical data by sex, and assessment of potential PK differences between women and men.[22] In 2001, the NIH further updated its policy on inclusion of women and minorities as subjects in clinical research, providing additional guidelines on planning, analysis, and reporting of potential sex/gender and racial/ethnic differences in phase III clinical trials.[23]

Despite accumulating scientific evidence for sex-related differences and the commitment of several federal agencies, little progress has been observed over the last 20 years in the participation of women in clinical research. Several studies investigating female participation in clinical research in various fields (eg, cardiovascular disease, cancer, and mental disorders) have reported a continued under-representation of women.[24–29] However, a systematic review of female participation in HIV clinical studies focusing on 3 aspects (cure research, vaccines, and antiretrovirals) has not yet been carried out.

In this systematic review, we examined women's participation in clinical studies of antiretroviral drugs (ARV), prophylactic HIV vaccine (VAX), and curative strategies (CURE) over time, to understand whether federal policies and guidelines have positively influenced women's inclusion in HIV clinical research. Furthermore, we investigated potential correlates of greater inclusion of women in these studies by looking at a number of factors including trial phase, source of funding, and country/ies where the study was conducted, ie, we focused on information provided in the reporting of these studies in the scientific literature.

METHODS

Search Strategy

To identify articles for analysis, PubMed searches were conducted using free text and medical subject headings listed in Table S1 (see Supplemental Digital Content, http://links.lww.com/QAI/A749). Included articles described clinical studies of ARV, VAX, and CURE in humans, in English. Detailed search strategies are described in the following sections below. All references represent the results from the completed study; observational studies, sub-studies, partial or preliminary results, and multiple trial results were excluded unless they represent the only results published. References in the retrieved articles with CURE interventions were, in addition, scanned to identify additional eligible publications on CURE. All full-text articles were manually retrieved that were found in the search and screened for eligibility criteria by 2 coauthors, and all cases of ambiguity were discussed further and resolved by consensus between all coauthors. Articles were included only if studies aimed to enroll both men and women above 18 years.

Clinical Trials With Antiretrovirals

For ARV clinical trials, the literature search targeted articles published during 3 periods (January 1, 1994–December 31, 1997, 2001–2004, and 2008–2011) in 8 peer-reviewed journals: *Lancet*, *Journal of Infectious Diseases*, *AIDS*, *AIDS Research and Human Retroviruses*, *New England Journal of Medicine*, *Journal of AIDS*, *Antimicrobial Agents and Chemotherapy*, and *Clinical Infectious Diseases*. The periods were chosen to sample representative literature of the period immediately after the introduction of the NIH *Revitalization Act* in 1993, with the assumption that trials whose findings were published in the first period were conducted before the introduction of the *Revitalization Act*. The journals were selected to represent high-impact specialized infectious diseases and general medical journals, in which ARV clinical trials are often published.

Clinical Trials With Vaccines

The search for articles describing HIV vaccine clinical trials was limited to randomized clinical trials in adults published from 2001 to 2012. Studies of therapeutic vaccines were excluded; they were included in the CURE dataset. All abstracts, regardless of journal, were reviewed to identify original research articles describing preventative AIDS vaccine randomized controlled trials.

Clinical Studies With HIV Curative Strategies

Studies of HIV CURE were included if the aim was to affect the persistence of HIV (eg, size or dynamics of the latent reservoir) and/or to improve the control of HIV in the absence of antiretroviral therapy. HIV CURE generally fall within 7 categories: analytic/structured treatment interruption; early treatment; gene therapy; immune therapy; therapeutic vaccination; treatment intensification; and viral reactivation. Articles that reported findings from studies of CURE and published from 1995 to 2012 were included. Considering the experimental nature of curative interventions, in addition to clinical trials, pilot studies, and studies where data/samples were collected from multiple trials were also included if they represented the only data available. This was also the reason why this search strategy differed slightly to the other 2 categories. In case of multiple publications from the same clinical study, only 1 publication describing the entire study population was retained in the final dataset.

Data Extraction

The following data were extracted for all 3 datasets: date of publication (if the issued date of publication was not available, the epub date was considered), study objectives, primary and secondary study outcomes, trial phase, clinical trial number and designation (if provided), funding source(s), and country/ies where the trial was conducted. Funding source was categorized into private commercial (eg, pharmaceutical company), private noncommercial (eg, universities, foundations), public (eg, federal agencies), and mixed (any combination) funding. Countries were categorized into low-, middle-, and

high-income countries according to the 2009 World Bank (http://data.worldbank.org/about/country-classifications/country-and-lending-groups) analytical income classification. Clinical trial phase was categorized further into early (phases I, I/II, II) and late (phases II/III, III, IV), where information on trial phase was lacking, if a clinical trial number was reported and information was retrieved from the corresponding database (www.clinicaltrials.gov). In addition, the number of women and total participants enrolled (defined as randomized or assigned to a study group, or provided informed consent) were recorded and proportions of women in each of the studies calculated. If data regarding the number of women enrolled were not indicated, numbers of women completing the study or reaching one of the defined endpoints, if available, were instead recorded. Studies that did not report the sex of participants at the enrollment or other stages of the study were excluded, even if number of women in the data analysis was reported. This was performed to reduce potential biases as there are various reasons why not all participants are included in analysis, which may be unrelated to participant's sex/gender (eg, sample could not be amplified). Only data reported in the articles were included. Authors were not contacted for further information.

Statistical Analysis

Statistical analyses were performed using the STATA statistical software (version 13.1; STATA Corporation, College Station, TX). The unit of analysis was the individual study. The proportion of female participants was defined as the number of women divided by the total participants for each trial. Data are typically presented as medians, percentages, and interquartile ranges (IQR). Associations of the proportion of female participation with year published, funding source, study country's income classification, clinical trials phase (or study size) were assessed using the Kruskal–Wallis, the Wilcoxon Rank-Sum tests, and Spearman rank test as appropriate. Where clinical trial phase was not available for all studies, the study sample size was dichotomized instead. For the ARV dataset with large-scale trials reported (phase IIb, III, or IV), the cutoff used to distinguish between small and large studies was set using the 75th percentile of the early phase trials (phase I, I/II, and IIa) plus half the difference between this number and the 25th percentile of the late-phase trials (phase IIb, III, and IV). Because early phase trials are usually smaller than late-phase trials due to the emphasis on safety versus efficacy, study size was considered an adequate alternative for analysis of association. For the CURE dataset, with no phase IIb, III, or IV trials, the median overall study size was used as the cutoff to dichotomize study size. Statistical significance was defined at $P < 0.05$. Where sample size permitted (ie, the ARV dataset), a multivariable linear regression model was built to characterize the independent associations of the aforementioned study characteristics with the proportion of female participation. Because the percentage of women enrolled was not normally distributed, we analyzed the square-root of percent female enrolled to assure that model assumptions were not violated.

RESULTS

Antiretroviral Clinical Trials

For ARV studies, 1028 articles were retrieved, of which 395 met the inclusion criteria (Table 1; see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/A749). Reasons for exclusion are shown in Table S2, (see Supplemental Digital Content, http://links.lww.com/QAI/A749). Furthermore, 8 articles were excluded from the analysis because no data on the total number of women were reported (n = 7) or only the sex distribution of the analyzed samples was available (n = 1). Of the total 95,305 participants enrolled in the ARV clinical trials analyzed here, 22,098 (23.2%) were women. Female participation in trials ranged from 0% to 94.5%, with a median of 19.2% (IQR 10.0%–30.1%). Eleven articles (2.8%) enrolled exclusively men, despite being eligible to both sexes (Table 1).

Of the 387 included articles, 33 were published in the period 1994–1997 (period I), 173 in 2001–2004 (period II), and 181 in 2008–2011 (period III). The median proportion of women in ARV clinical trials increased significantly from 8.8% during period I to 18.2% during period II and to 21.6% during period III ($P = 0.0001$) (Fig. 1A).

As over 60% of studies considered did not report trial phase, trial size was used as a proxy for defining early versus late clinical trials. Smaller trials (<125 participants) tended to include proportionally fewer women (median: 18.4%, IQR 8.5%–29.4%) than larger trials (>124 participants; median: 20.4%, IQR 13.6%–31.7%) ($P = 0.01$) (Fig. 2A).

Most studies were conducted in high-income countries (n = 313; 80.9%). In case of 28 studies, these were conducted in low- and middle-income countries, and 38 studies enrolled volunteers across countries with different income categories (low/middle and high); 8 were missing these data. Country

TABLE 1. Study Populations and Proportion of Women Across ARV, VAX, and CURE Clinical Studies

	No. Articles Reporting Recruitment of Adult Men and Women	Articles Reporting Sex of Participants, N (%)*	Articles Reporting Zero Women Participants, N (%)	Women/Total Participants Overall, N (%)	Median (Range) of Female Participation Within Each Study, %
ARV	395	387 (98.0)	11 (2.8)	22,098/95,305 (23.2)	19.2 (0–94.5)
VAX	63	53 (84.1)	0 (0.0)	10,303/33,073 (31.2)	38.1 (5.7–66.7)
CURE	132	103 (78.8)	29 (27.9)	3356/15,655 (21.4)	9.9 (0–88.9)

*Articles that reported sex of enrolled participants (randomized/assigned/those that provided consent), of participants who started the intervention (baseline characteristics) or of participants who completed or reached a study endpoint. This represents the denominator for our analyses and for all cells to the right.

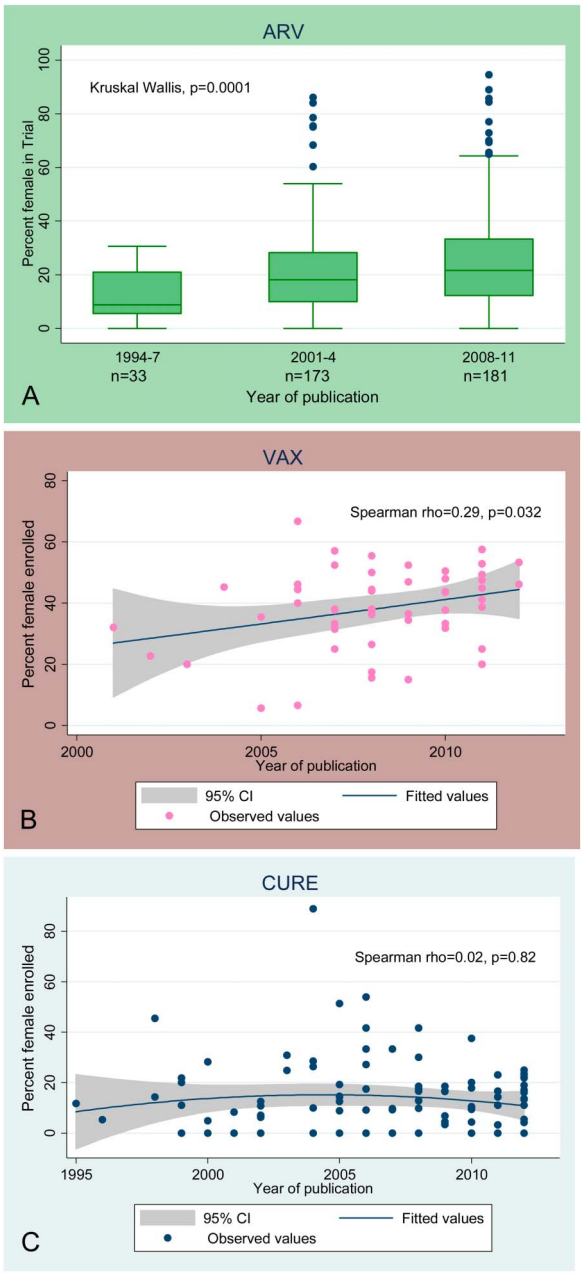

FIGURE 1. A–C, Percentage of women over publication years (horizontal bars are median values, box represents the IQR, whiskers the upper and lower adjacent values, and outliers shown as dots). ARV, antiretroviral drugs; CI, confidence interval; CURE, curative strategies; VAX, prophylactic vaccines.

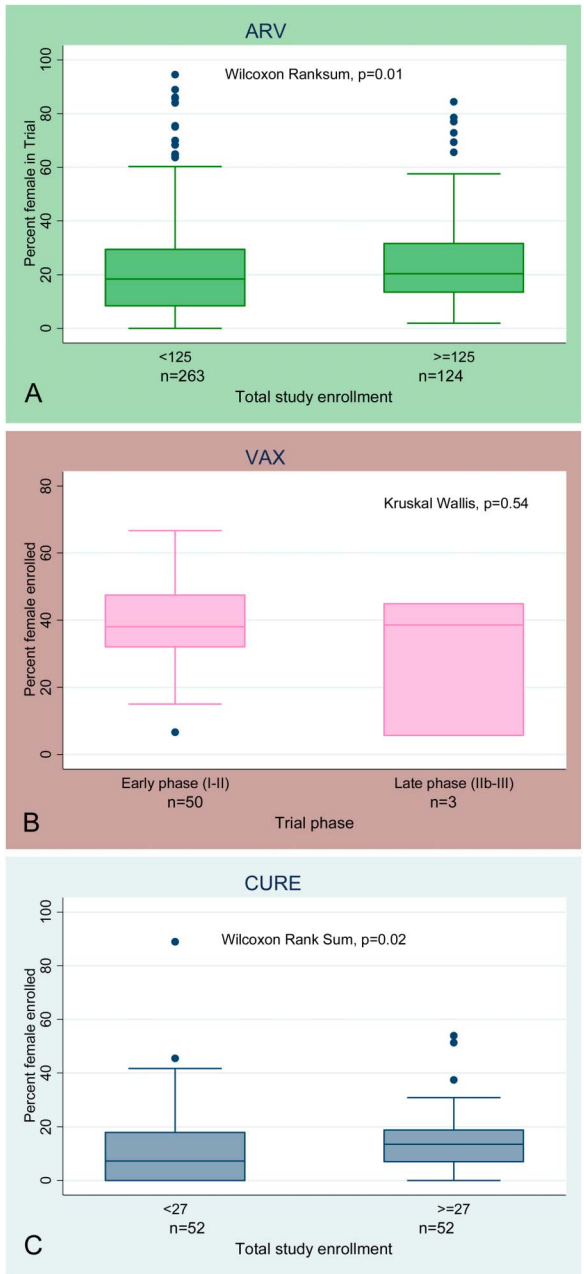

FIGURE 2. A–C, Percentage of women versus size of study (horizontal bars are median values, box represents the IQR, whiskers the upper and lower adjacent values, and outliers shown as dots). ARV, antiretroviral drugs; CURE, curative strategies; VAX, prophylactic vaccines.

income classification was significantly associated with female participation ($P = 0.0001$) (Fig. 3A) with 50.0% participation in low-and middle-income countries compared with 18.0% in high income and 23.2% in mixed.

The source of funding was available for 316 studies, and female participation in ARV trials was significantly correlated with funding source ($P = 0.03$) (Fig. 4A). Studies funded by private, noncommercial sources had the highest proportion of women with a median of 29.2% (IQR 21.25%–47.6%), whereas publicly funded trials had the lowest with a median of 16.7% (IQR 10%–27%). Studies with funding from private, commercial sources, or from a combination of public and private sources had a median of 19.3% (IQR 10.0%–29.4%) and 19.8% (IQR 10.2%–30.85%) women, respectively. We recorded 96 (30.4%) studies funded by the NIH, nearly half of which were cofunded by other funding sources. The median proportion of women in trials funded fully or partially by the NIH reached 19.6% (IQR

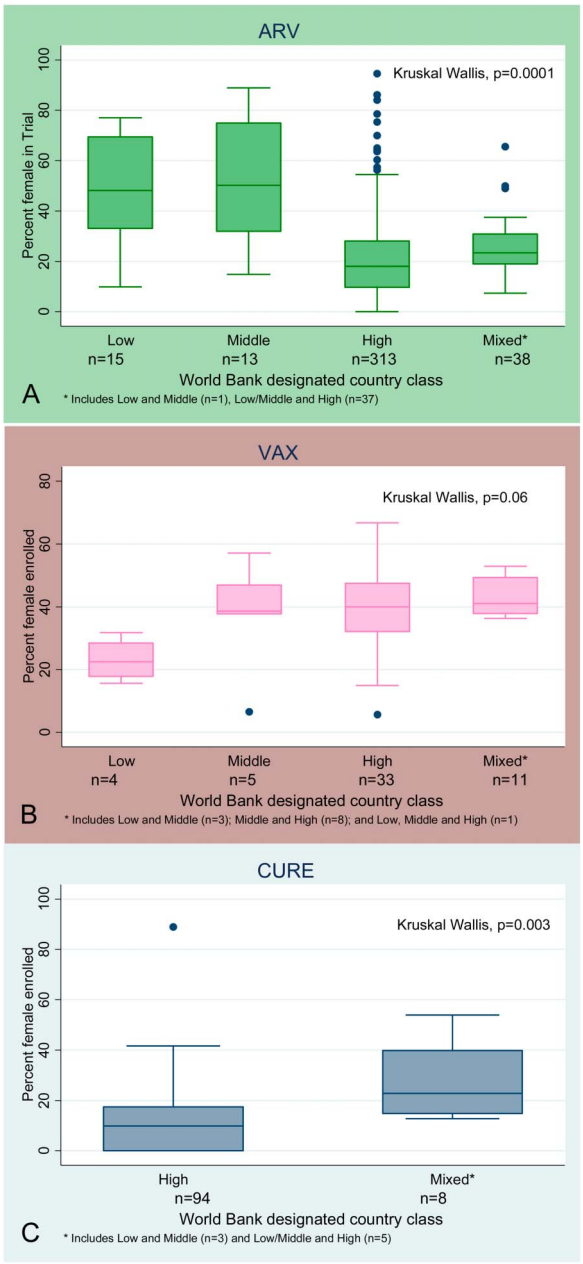

FIGURE 3. A–C, Percentage of women versus study country income class (horizontal bars are median values, box represents the IQR, whiskers the upper and lower adjacent values, and outliers shown as dots). ARV, antiretroviral drugs; CURE, curative strategies; VAX, prophylactic vaccines.

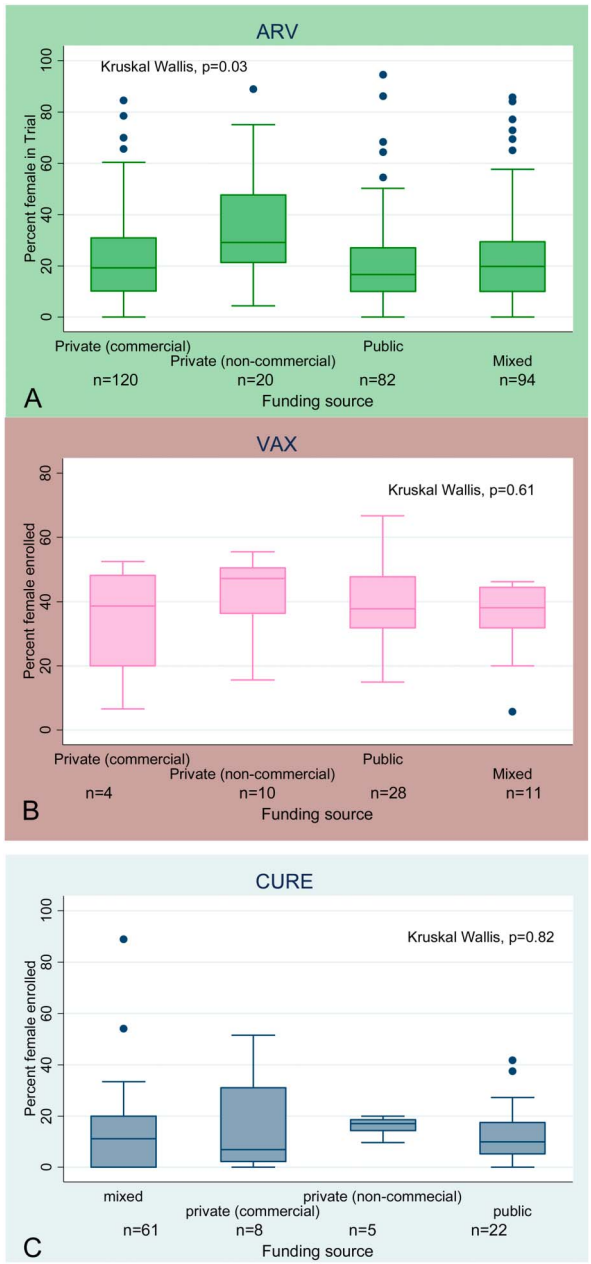

FIGURE 4. A–C, Percentage of women versus funding source (horizontal bars are median values, box represents the IQR, whiskers the upper and lower adjacent values, and outliers shown as dots). ARV, antiretroviral drugs; CURE, curative strategies; VAX, prophylactic vaccines.

9.10%–23.8%), significantly lower than the 22.3% (IQR 11.8%–32.7%) for trials funded by sources other than NIH ($P = 0.001$) (see Figure S2, Supplemental Digital Content, http://links.lww.com/QAI/A749).

The ARV dataset was of ample size to permit multivariable analysis of predictors of female enrollment (see Table S3, Supplemental Digital Content, http://links.lww.com/QAI/A749). Later publication years were significantly associated with an increased likelihood of greater proportional female participation ($P = 0.002$ for period II and $P = 0.0001$ for period III). Compared with private noncommercial funding, studies funded with private (commercial) funds including mixed funding ($P = 0.02$) and public funds (including NIH) ($P = 0.003$) were all less likely to enroll women. The strongest correlate with low proportions of women enrolled was the country income class where the study was conducted. Studies conducted in high income or high and other (either low or medium) were significantly less likely to enroll high

proportions of women ($P = 0.0001$). A smaller trial size was not significantly ($P = 0.10$) associated with lower female enrollment, but also confounded other relationships, and was thus kept in the model.

VAX Clinical Trials

The PubMed search retrieved a total of 79 articles, of which 53 were included in the final dataset (see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/A749). Reasons for exclusions are outlined in Table S2 (see Supplemental Digital Content, http://links.lww.com/QAI/A749). Overall, 33,073 participants were reported, of whom 10,303 (31.2%) were women (Table 1). Female participation ranged from 5.7% to 66.7% with a median of 38.1% (IQR 32.1–46.9). As in the ARV studies, a significant increase in the proportion of women over time was observed ($P = 0.03$) (Fig. 1B).

Although our sample size was modest, early phase trials (I–I/IIa, n = 50) had a similar median proportion of female participation (38.1%, IQR 32.1%–47.5%) compared with 38.6% (IQR 5.7%–44.9%) in late-phase trials (IIb–III, n = 3) ($P = 0.54$) (Fig. 2B).

VAX studies conducted in low-income countries (n = 4) had a lower proportion of women (median: 22.5%; IQR 17.8–28.4) than those conducted in high- and middle-income countries (n = 38; median: 39.3%; IQR 32.1–47.5) ($P = 0.06$, Fig. 3B). No significant association between the proportion of women in VAX trials and category of funding source was observed ($P = 0.61$, Fig. 4B).

HIV Cure Clinical Trials

The literature search for CURE studies resulted in 146 articles, of which 104 studies (103 articles) were included in the final dataset (see Table S2 and Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/A749). Of a total 15,655 participants, 3356 (21.4%) were women including 1 volunteer reporting male-to-female sex reassignment (the only transgender study participant reported in any included article). Within each study, this ranged from 0% to 88.9% (median: 11.1%, IQR 0%–18.8%). Twenty-nine studies (27.9%) reported no women enrolled, despite the eligibility of both sexes. There was no observed increase in the proportion of women in CURE studies over time ($P = 0.82$) (Fig. 1C).

Only 29 (27.8%) studies reported trial phase, none of which were phase IIb or III. The median size of all CURE studies was 27 participants; smaller studies (<27 participants) were significantly more likely to have proportionally fewer women than larger studies (median: 7.3%, IQR: 0–18.0 vs. 13.5%, IQR: 7.0–18.8, respectively, $P = 0.02$) (Fig. 2C).

Most CURE studies was carried out in high-income countries (n = 94), 3 studies were conducted in low- and middle-income countries, and 5 were conducted in high and either middle- or low-income countries (2 studies did not provide location data). The 8 studies conducted in countries of different incomes had higher proportions of female participants (median: 22.9%, IQR: 14.9–39.8) compared with those conducted solely in high-income countries (9.9% IQR: 0–17.5, $P = 0.003$) (Fig. 3C).

Most of the included CURE studies were funded through a combination of funding sources (n = 61) or through public funding (n = 22). Eight studies did not provide funding details. The proportion of women did not differ between studies with different categories of funding ($P = 0.82$) (Fig. 4C).

DISCUSSION

Although women represent half of the HIV-infected population worldwide,[30] they continue to be underrepresented in HIV clinical trials. Despite a significant increase in the proportion of women in clinical trials testing ARVs and VAX over the years, the overall median remained low at 19.2% and 38.1%, respectively. Women were most poorly represented in studies investigating CURE (median: 11.1%), a number that has not markedly improved over time. HIV cure research is an emerging line of inquiry, suggesting that cure studies are more experimental in nature, which in turn may explain—although not justify—the low numbers of women. Low female representation in phase I trials has been reported by Pinnow et al[28] previously (2009).

Our study confirms previous similar observations about low female participation in HIV trials. A study of New Drug Application (NDA) trials sponsored by pharmaceutical companies and submitted 2000–2008 revealed a female participation rate of around 20%.[31] A systematic review of 49 randomized and controlled clinical trials of antiretroviral treatments indexed in the Cochrane Controlled Trials Register between 1990 and 2000 reported a mean of 12.3% female participation.[32] This number is consistent with our findings for 1994–1997 and 2000–2004 (median: 8.8% and 18.2%, respectively), reflecting an increasing trend in the enrollment of women in ARV trials over the past 20 years, although female representation has not reached parity.

Low female participation has also been observed in studies focusing on cardiovascular disease, cancer, pain therapies, and the treatment of depression.[25,29,33–37] In addition, a recent study tracking women's participation in late-phase (II, II/III and III) clinical trials for FDA NDAs reported that between 2007 and 2009, the total female participation was 43%, with no significant increasing trend since 1998 (Poon et al, 2013). The 3 antiviral NDAs in this study averaged 12% women, one of the lowest percentages across all study categories. The lower percentage of women in antiviral studies in this study versus ours (12.0% vs. 19.2%) suggest that the safety concerns related to investigational new drug may play a role in women's willingness (or ability) to participate or may discourage researchers from enrolling them.

Despite efforts to address the sex bias in clinical research through regulations and policies such as the *Revitalization Act* in the US, the sex gap in HIV clinical studies persists. The results from our ARV dataset demonstrate that publicly funded studies continue to enroll insufficient number of women. In fact, ARV trials that were fully or partially sponsored by NIH included a significantly lower proportion of women compared with studies funded by other

sources, indicating that the US federal regulations have limited impact on the inclusion of women in ARV clinical trials.

This discrepancy may not be generalized across medical disciplines. A study investigating the representation of women in cardiovascular preventive trials showed that female enrollment was comparable in government/foundation-funded versus industry-funded trials.[36] By contrast, an analysis of cancer clinical research in 8 high impact journals yielded more women in government-funded studies.[25] A previous study looking at clinical trials funded by the US federal agencies across medical disciplines reported similar results, showing a median of 37% female enrollment in studies conducted in 2009.[24]

Our literature review additionally provides insight into study characteristics, which may be associated with female participation in clinical research. In this study, country income classification played a role in the proportion of women enrolled. Studies in low- and middle-income countries were associated with significantly higher female participation in ARV and CURE clinical studies. By contrast, lower female participation in VAX studies was observed in low-income countries. This discrepancy could in part be due to a higher prevalence of HIV among women in certain low- and middle-income countries such as those in sub-Saharan Africa.[30] At the same time, the epidemic in high-income countries mostly affects men who have sex with men. In the United States, for instance, men who have sex with men accounted for 63% of all new HIV infections in 2010 and 52% of all people living with HIV in 2009.[38] The pattern of HIV epidemiology may reflect the ease or the motivation of men and women to participate in clinical studies with antiretroviral trials and/or CURE in their respective countries/regions.

Many trial- or context-specific barriers hinder the participation of women in clinical research.[26,39] Structural factors such as poor socio-economic conditions, sex inequality and low education negatively affect female participation. To note, in our study, nearly all of the articles included were very cursory in their discussions of the study population(s), and therefore important variables such as race/ethnicity and socioeconomic status were not included. Additional details on race/ethnicity, socio-economic factors, and other demographics, particularly in larger phase III trials, could allow for even greater insight.

A lack of understanding of what clinical trials are or awareness of opportunities to participate can also decrease female participation and perceived barriers regarding time commitment needed and costs of participation.[40] In addition, women are often primary caregivers, which may render them less available to participate in trials.[41] Concerns over pregnancies during trials and unintended consequences to the fetus continue to be of concern, although more comprehensive family planning education and provision of contraception could address some of these challenges.[42] Moreover, requiring female participants to use contraception consistently during the study period can be challenging in cultures where women's fertility is an important societal factor, or self-efficacy is limited.[39] The increasing availability of long acting, user-independent methods of birth control such as intrauterine contraceptive device and implants may serve to improve female participation in certain contexts.

The GRACE study, which systematically included women in a phase III ARV clinical trial, demonstrated that taking female-specific barriers into consideration during the initial stages of a study can increase participation—the study achieved a female inclusion rate of 67%, which was mainly attributed to careful planning and research of the local context (epidemiologic trends and identification of study sites) and to the engagement of community advocates and advisors and individualized consulting support for each site. This study highlighted that including women in research is not just a matter of enrolling women but requires tailored recruitment strategies. However, the discontinuation rate in this trial was higher among women than men, demonstrating that participation relies not only on recruitment but also retention.[43]

One limitation of this study is that all 3 searches focused on published research indexed in PubMed, but this may not represent a complete assessment of female trial enrollment. The 3 searchers did not fully overlap in their time span and therefore, direct comparisons between the findings were performed cautiously in this study. Unpublished HIV clinical studies were not considered, and for the ARV dataset, the search was restricted to specific periods and journals, although the sample is sufficiently representative of the literature. Furthermore, as searches were focused on defined PubMed terms (see Table S1, Supplemental Digital Content, http://links.lww.com/QAI/A749), there may have been published studies that our search strategy did not retrieve. This is particularly relevant for the CURE dataset, as the term "cure" is often not listed as a keyword. Thus, other terms which capture the CURE strategies field were used, but the list used may not have been exhaustive.

CONCLUSIONS

Our study showed a persistent under-representation of women in HIV clinical trials. Addressing the sex bias in biomedical research remains an urgent priority for both research and public health. Only with sufficient knowledge of sex and gender differences and similarities can optimal and evidence-based treatment, prevention, and care be delivered to both women and men living with or at risk for HIV. Despite different sex profiles of the HIV epidemic in countries across the world, HIV research should strive to be generalizable and particular efforts to recruit subpopulations even in settings where one sex is overrepresented among people living with HIV is an important aspect of effective research strategies.

All research stakeholders need to be actively engaged to achieve progress toward satisfactory sex balance and meaningful sex- and gender-based analysis in research. In their infancy, trials must be designed with this goal in mind, including recruitment quotas and context-specific planning. Reviewers of funding applications and publications should ensure that adequate female representation has been addressed. Journal editors should enact a strict policy for

reporting female representation, and lastly, funding bodies should require and enforce adequate female participation.

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REFERENCES

1. Cook MB, Dawsey SM, Freedman ND, et al. Sex disparities in cancer incidence by period and age. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:1174–1182.
2. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. *Am J Pathol.* 2008;173: 600–609.
3. McClelland EE, Smith JM. Gender specific differences in the immune response to infection. *Arch Immunol Ther Exp (Warsz).* 2011;59: 203–213.
4. Regitz-Zagrosek V. Sex and gender differences in health. Science & society series on sex and science. *EMBO Rep.* 2012;13:596–603.
5. Gandhi M, Aweeka F, Greenblatt RM, et al. Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol.* 2004;44:499–523.
6. FDA. Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). 2013. Available at: www.fda.gov/downloads/Drugs/DrugSafety/UCM335007.pdf. Accessed May 20, 2015.
7. Umeh OC, Currier JS. Sex differences in pharmacokinetics and toxicity of antiretroviral therapy. *Expert Opin Drug Metab Toxicol.* 2006;2: 273–283.
8. Gesensway D. Reasons for sex-specific and gender-specific study of health topics. *Ann Intern Med.* 2011;135:935–938.
9. Krieger N. Genders, sexes, and health: what are the connections–and why does it matter? *Int J Epidemiol.* 2003;32:652–657.
10. Pinn VW. Sex and gender factors in medical studies: implications for health and clinical practice. *JAMA*. 2003;289:397–400.
11. Padian NS, Shiboski SC, Glass SO, et al. Heterosexual transmission of human immunodeficiency virus (HIV) in northern California: results from a ten-year study. *Am J Epidemiol.* 1997;146:350–357.
12. Gandhi M, Bacchetti P, Miotti P, et al. Does patient sex affect human immunodeficiency virus levels? *Clin Infect Dis.* 2002;35:313–322.
13. Jarrin I, Geskus R, Bhaskaran K, et al. Gender differences in HIV progression to AIDS and death in industrialized countries: slower disease progression following HIV seroconversion in women. *Am J Epidemiol.* 2008;168:532–540.
14. Cornell M, Schomaker M, Garone DB, et al. Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: a multicentre cohort study. *PLoS Med.* 2012;9:e1001304.
15. Druyts E, Dybul M, Kanters S, et al. Male sex and the risk of mortality among individuals enrolled in antiretroviral therapy programs in Africa: a systematic review and meta-analysis. *AIDS*. 2013;27:417–425.
16. Maskew M, Brennan AT, Westreich D, et al. Gender differences in mortality and CD4 count response among virally suppressed HIV-positive patients. *J Womens Health (Larchmt).* 2013;22:113–120.
17. Ofotokun I, Pomeroy C. Sex differences in adverse reactions to antiretroviral drugs. *Top HIV Med.* 2003;11:55–59.
18. Elzi L, Marzolini C, Furrer H, et al. Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008. *Arch Intern Med.* 2010;170: 57–65.
19. Berlin JA, Ellenberg SS. Inclusion of women in clinical trials. *BMC Med.* 2009;7:56.
20. Parekh A, Fadiran EO, Uhl K, et al. Adverse effects in women: implications for drug development and regulatory policies. *Expert Rev Clin Pharmacol.* 2011;4:453–466.
21. NIH. *S.1-National Institutes of Health Revitalization Act of Subtitle B–Clinical Research Equity Regarding Women and Minorities Part I–Women and Minorities as Subjects in Clinical Research*. Washington, DC; NIH: 1993.
22. FDA. *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation in Drugs*. Washington, DC; FDA: 1993.
23. NIH. *NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research—Amended, October, 2001*. Washington, DC; NIH: 2001.
24. Geller SE, Koch A, Pellettieri B, et al. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? *J Womens Health (Larchmt).* 2011;20:315–320.
25. Jagsi R, Motomura AR, Amarnath S, et al. Under-representation of women in high-impact published clinical cancer research. *Cancer*. 2009; 115:3293–3301.
26. Kim ESH, Menon V. Status of women in cardiovascular clinical trials. *Arterioscler Thromb Vasc Biol.* 2009;29:279–283.
27. Poon R, Khanijow K, Umarjee S, et al. Participation of women and sex analyses in late-phase clinical trials of new molecular entity drugs and biologics approved by the FDA in 2007-2009. *J Womens Health (Larchmt).* 2013;22:604–616.
28. Pinnow E, Sharma P, Parekh A, et al. Increasing participation of women in early phase clinical trials approved by the FDA. *Womens Health Issues.* 2009;19:89–93.
29. Weinberger AH, McKee S, Mazure CM. Inclusion of women and gender-specific analyses in randomized clinical trials of treatments for depression. *J Womens Health (Larchmt).* 2010;19:1727–1732.
30. UNAIDS. *Global Report. UNAIDS Report on the Global AIDS Epidemic 2013*. Geneva, Switzerland; UNAIDS: 2013.
31. Soon GG, Min M, Struble K, et al. Meta-analysis of gender differences in efficacy outcomes for HIV-positive subjects in randomized controlled clinical trials of antiretroviral therapy (2000-2008). *AIDS Patient Care STDS.* 2012;26:444–453.
32. Pardo MA, Ruiz MT, Gimeno A, et al. Gender bias in clinical trials of AIDS drugs. Abstract ID 6508. Paper presented at: The XIV International AIDS Conference; Barcelona, Spain, July 7–12, 2002.
33. Chilet-Rosell E, Ruiz-Cantero MT, Horga JF. Women's health and gender-based clinical trials on etoricobix: methodological gender bias. *J Public Health.* 2009;31:434–445.
34. Johnson SM, Karvonen CA, Phelps CL, et al. Assessment of analysis by gender in the cochrane reviews as related to treatment of cardiovascular disease. *J Womens Health (Larchmt).* 2003;12:449–457.
35. Kim ESH, Carrigan TP, Menon V. Enrollment of women in National Heart, Lung, and Blood Institute-funded cardiovascular randomized controlled trials fails to meet current federal mandates for inclusion. *J Am Coll Cardiol.* 2008;52:672–673.
36. Melloni C, Berger JS, Wang TY, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. *Circ Cardiovasc Qual Outcomes.* 2010;3:135–142.
37. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA*. 2004;291: 2720–2726.
38. CDC. *HIV in the United States: At A Glance*. Washington, DC; CDC: 2013:5.
39. Mills E, Nixon S, Singh S, et al. Enrolling women into HIV preventive vaccine trials: an ethical imperative but a logistical challenge. *PLoS Med.* 2006;3:e94.
40. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. *Cancer*. 2008;112:228–242.
41. Stein MD, Crystal S, Cunningham WE, et al. Delays in seeking HIV care due to ompeting caregiver responsibilities. *Am J Public Health.* 2002;90: 1138–1140.
42. Van Spall HGC, Toren A, Kiss A, et al. Eligibility criteria of randomized controlled trials published in high-impact general medical journals. A systematic sampling review. *JAMA*. 2007;297:1233–1240.
43. Falcon R, Bridge DA, Currier J, et al. Recruitment and retention of diverse populations in antiretroviral clinical trials: practical applications from the gender, race and clinical experience study. *J Womens Health (Larchmt).* 2011;20:1043–1050.