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Phase 3 trials of new antiretrovirals are not representative of the global HIV epidemic

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Abstract

Introduction: People living with HIV (PLWH) are mainly African or Asian, the majority female. In contrast, pharmaceutical companies typically conduct phase 3 regulatory randomised controlled trials (RCTs) in high-income countries (HICs), where PLWH are mainly white males. Regulatory authorities can be conservative about including pregnant women in trials, discouraging female participation. Some adverse events occur more frequently by sex or by race because of differing pharmacokinetics. Most drugs have insufficient safety data in pregnancy and non-white people even after regulatory approval. The present study compared race and sex demographics of phase 3 RCTs of dolutegravir (DTG), bictegravir (BIC) and tenofovir alafenamide (TAF) with global HIV epidemic demography.

Methods: National epidemic sizes by sex were extracted from UNAIDS 2018 data. National demographics were used to estimate prevalence by race. PLWH by national socio-economic status were calculated from World Bank data. Summary race and sex demographic data for 10 phase 3 trials of DTG ($n = 7714$), four of BIC ($n = 2307$), eight of TAF ($n = 7573$) and two of doravirine (DOR) ($n = 1407$) were extracted from ClinicalTrials.gov.

Results: Black females (42%) and black males (30%) have highest prevalence globally. White males comprise 6% of PLWH. Over 60% of PLWH live in low or low-middle-income countries, 68% of whom are black and 23% Asian. Seventy-six per cent of DTG trial centres were in high-income countries (HICs) (5% global burden) and 23% in upper-middle-income countries (UMICs). DTG trials were not representative of PLWH even within the UMIC and HIC setting (49% white male *vs* 31% income band). White males were overrecruited by 44% to DTG, BIC, TAF and DOR trials in comparison with prevalence. Black females were underrepresented by 35%.

Conclusion: Phase 3 RCT populations for new antiretrovirals comprised 51% white males, vastly disproportionate to the global HIV epidemic (6%). Females and non-white people are underrepresented. Female safety data are insufficient despite drug approval in Europe and USA. HIV trials should be located in regions representing the global epidemic with no sex-based selection. Trials should aim for at least 50% female and 50% non-white recruitment to properly provide safety information.

Keywords: clinical trials, HIV, black females, antiretrovirals, phase 3

Introduction

Over the past 30 years of HIV drug development, there have been several serious safety issues only discovered several years after regulatory approval. These safety issues include lipoatrophy on stavudine, suicidality on efavirenz and clinical obesity on integrase inhibitors, particularly in combination with tenofovir alafenamide (TAF) and emtricitabine (FTC).

Pharmaceutical companies design development programmes for new antiretrovirals, which typically include two large phase 3 randomised trials. These trials usually evaluate safety and efficacy for at least 500 participants treated for at least 48 weeks with the new antiretroviral, against current standard of care. The combined safety database from these phase 3 trials is typically the main component of a regulatory submission to the US Food and Drug Administration or regulatory authorities in other countries.

Rare safety endpoints can often only be detected after several thousand people have been treated with a new antiretroviral. It could be inevitable that some safety issues are only discovered after initial drug approval, once wider clinical experiences are compiled. However, several key adverse event (AE) risks differ significantly by race and sex. For example, efavirenz pharmacokinetics are different between black and white people, which can lead to more central nervous system AEs [1,2]. Women are at higher risk of hepatotoxicity of nevaripine, which could be associated with different pharmacokinetics by sex [3,4]. Women are at higher risk of lactic acidosis on stavudine [5]. The HLA-B*5701 haplotype is more common in white people, which confers risk for an abacavir hypersensitivity reaction [6]. The risk of clinical obesity on integrase inhibitors is higher for black than for white people, and also higher for women than for men [7]. Our ability to compare AEs by race and sex would improve if phase 3 trials were more inclusive of women and non-white people.

The purpose of this analysis was to evaluate race and sex demographics in phase 3 randomised controlled trial (RCT) programmes of four recently approved antiretrovirals: dolutegravir (DTG), bictegravir (BIC), TAF and doravirine (DOR). The results were compared with the UNAIDS worldwide database to assess phase 3 RCT demographics in proportion to the global epidemic.

Methods

National HIV epidemic sizes by sex were extracted from UNAIDS 2018 data [8]. National demographics were used to estimate the prevalence of HIV by race. The number of people living with HIV

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(PLWH) by national socio-economic status were calculated from World Bank data [9]. Race and sex demographics for 10 phase 3 trials of DTG (n = 7714) [10–19], four of BIC (n = 2307) [20–23], eight of TAF (n = 7573) [24–31] and two of DOR (n = 1407) [32,33] were extracted from published studies and the online database ClinicalTrials.gov, which shows standardised reports for all pharmaceutical company–sponsored phase 3 trials that have been completed. Race was divided into white, black and other. Proportions in each sex and race category were estimated by multiplying the percentage of people of each sex by the percentage of each race. RCT databases had insufficient details to further divide the 'other' race category into Asians, Pacific Islanders or more.

Results

Roughly 42% of the global population of PLWH were black female and 30% black male; around 3% were white female and 6% white male (Figure 1; Table 1). Twelve per cent were females of another race and 7% male (Table 1). In contrast, from registration RCTs of DTG, BIC, TAF and DOR, an aggregate 7% of participants were black female, 17% black male, 13% white female and 50% white male. This trend was consistent across trials for all four drugs (Table 2). On average, 45%–53% white males and 3%–11% black females were recruited (Table 1). White males were overrecruited by an average of 44%, whereas black females were underrecruited by 35%.

Table 1. Estimated global demographics of PLWH *vs* RCT demographics. Percentages may be rounded up to make 100.

		Global (%)	DTG trials, *n* (%)		BIC trials, *n* (%)		TAF trials, *n* (%)		DOR trials, *n* (%)	
Black	Female	42	530	(7)	232	(11)	558	(7)	35	(3)
	Male	30	1151	(15)	479	(21)	1299	(17)	189	(14)
White	Female	3	1062	(14)	321	(14)	1233	(16)	132	(9)
	Male	6	4048	(53)	1022	(45)	3768	(49)	722	(51)
Other	Female	7	237	(3)	111	(5)	301	(4)	48	(4)
	Male	12	639	(8)	83	(4)	591	(7)	264	(19)

BIC: bictegravir; DOR: doravirine; DTG: dolutegravir; PLWH: people living with HIV; RCT: randomized controlled trial; TAF: tenofovir alafenamide.

Table 2. Estimated clinical trial demographics by sex and race

Drug	Trial	*n*	Black		White		Other	
			Women (%)	Men (%)	Women (%)	Men (%)	Women (%)	Men (%)
DTG	SINGLE [10]	833	3.8	19.8	10.9	57.3	1.3	6.7
	FLAMINGO [11]	484	3.5	20.0	10.7	61.4	0.6	3.3
	ARIA [12]	495	42.4	0.0	44.8	0.0	12.7	0.0
	GEMINI [13]	1433	1.9	10.7	10.0	58.0	2.9	17.0
	SPRING-2 [14]	822	1.6	9.1	12.3	72.6	0.6	3.8
	TANGO [15]	741	1.2	13.8	5.7	73.0	0.4	5.5
	SWORD [16]	1014	1.8	6.3	18.0	62.8	2.0	7.2
	STRIIVING [17]	553	4.0	24.0	9.2	56.6	0.4	1.6
	DAWNING [18]	624	13.6	25.3	10.3	18.8	11.2	20.8
	SAILING [19]	715	13.6	28.5	15.8	33.2	2.5	5.5
BIC	Gilead 1489 [20]	629	3.4	32.4	5.6	51.4	0.6	6.4
	Gilead 1490 [21]	645	3.6	26.4	7.0	51.9	0.3	2.3
	Gilead switch [22]	563	2.3	18.7	8.3	64.7	0.5	5.0
	Gilead women [23]	470	37.0	0.0	41.2	0.0	21.7	0.0
TAF	AMBER [24]	625	1.3	9.8	9.9	73.1	0.8	6.1
	EMERALD [25]	1141	3.8	17.2	13.5	61.5	0.7	3.5
	366-1160 [26]	875	23.5	3.5	58.2	8.7	5.1	0.8
	366-1216 [27]	630	1.9	17.1	7.5	67.4	0.6	5.9
	311-1089 [28]	663	3.0	16.9	11.2	62.1	7.5	2.6
	292-0109 [29]	1436	2.0	29.5	7.4	59.6	1.5	12.5
	380-1961 [30]	470	37.0	0.0	28.0	0.0	35.1	0.0
	292-0104/0111 [31]	1733	3.8	21.2	8.5	48.5	2.7	15.2
DOR	DRIVE-AHEAD [32]	734	2.9	15.4	7.2	39.6	5.2	28.0
	DRIVE-SHIFT [33]	673	2.1	12.3	11.7	64.0	1.6	8.5

BIC: bictegravir; DOR: doravirine; DTG: dolutegravir; TAF: tenofovir alafenamide.

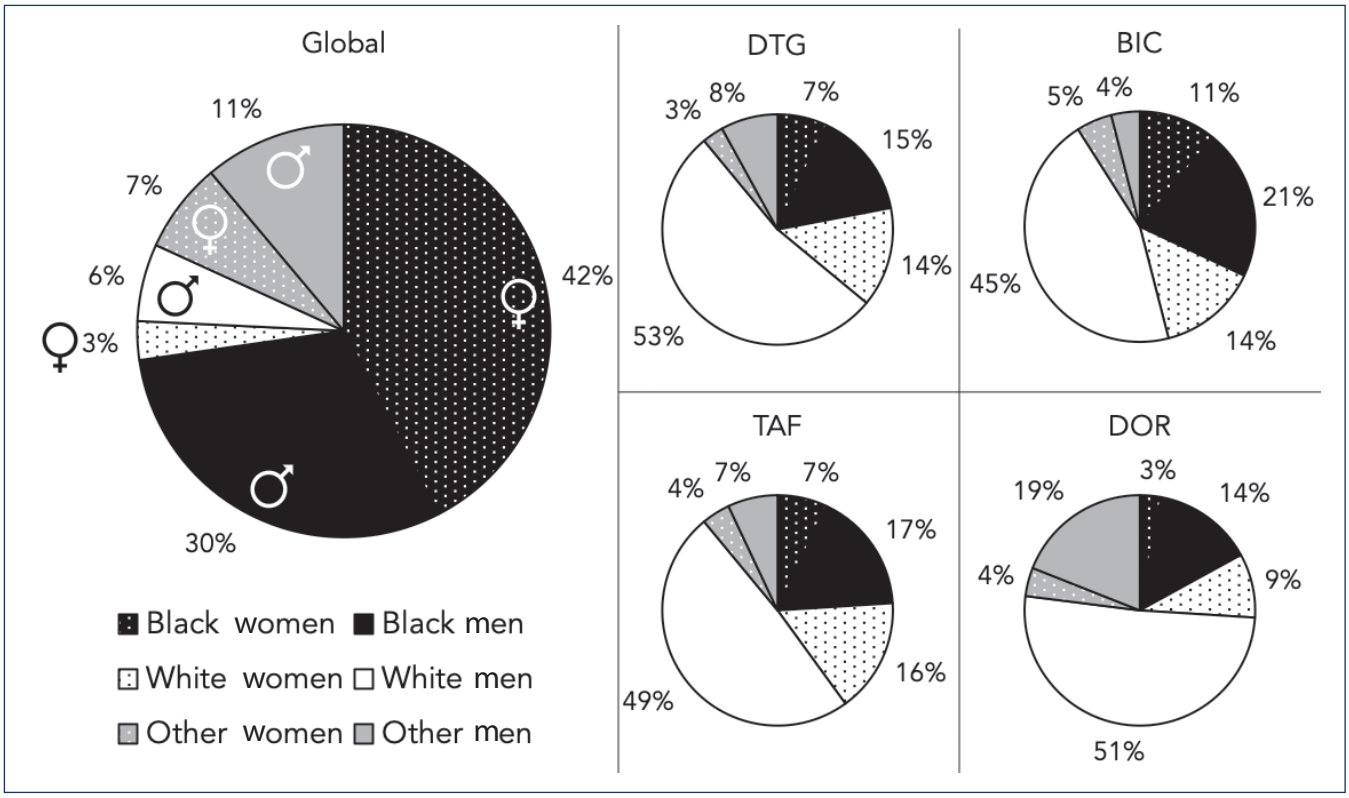

Figure 1. Estimated global demographics of PLWH *vs* RCT demographics. Percentages may be rounded up to make 100. Data are given as percentage. BIC: bictegravir; DOR: doravirine; DTG: dolutegravir; PLWH: people living with HIV; RCT: randomised controlled trial; TAF: tenofovir alafenamide.

Over 60% of PLWH live in low or low-middle-income countries (LIC or LMICs), 91% of whom are non-white (68% black, 23% Asian). Conversely, 76% of centres in the DTG trials analysed were in high-income countries (HICs), which bear 5% of the global burden, and 23% in upper-middle-income countries (UMICs). However, the location of trial centres does not fully explain the observed bias in RCT demographics. Only 31% of PLWH in UMIC and HICs are white male compared with 50.2% across trials for the antiretrovirals assessed, meaning that these RCTs are unrepresentative of the population from which their participants are drawn, which itself is unrepresentative of the global epidemic.

Discussion

Our analysis indicates that regulatory RCTs for novel antiretrovirals are vastly unrepresentative of PLWH globally. White men were overrecruited by around 44% compared with their global burden of disease, while black women were underrecruited by around 35%.

Groups at highest risk of serious safety issues are being underrecruited. This could impact drug safety profiles as shown by the 48-week results of the ADVANCE trial, an ongoing phase 3 trial of DTG *vs* EFV standard of care based in Johannesburg, South Africa, which recruited 59% black women. Despite a number of existing pharmaceutical company trials, the ADVANCE trial found novel results regarding dangerous levels of clinical obesity in South African women on DTG, especially with a TAF and FTC backbone [7].

Due to a market-led research model, pharmaceutical companies typically draw participants from convenient populations that are able to pay a higher price for life-saving drugs. Seventy-six per cent of DTG trial centres are in HICs, bearing only 5% of the global burden of HIV. Setting may be as important as population as a growing body of evidence suggests that social environment pervasively impacts all aspects of health care [34]. RCTs are typically run in sub-Saharan Africa after the initial trials have been completed mainly in North America and Europe. This practice leads to delays in our understanding of drug safety. ViiV sponsorship of the ARIA trial, which recruited 42.4% black women, is a stand-out example of how pharmaceutical companies can provide a more balanced picture of drug safety.

This analysis is a step towards more equitable research practices for RCTs of novel ART. Two researchers reviewed RCT race and sex demographics and independently calculated average demographics for each drug. The trials included in this analysis were all large, widely cited, regulatory RCTs. However, estimates were limited by the assumption of consistent distribution of sex by race. Global prevalence by race and sex was difficult to estimate due to high levels of uncertainty in UNAIDS 2018 data and in national racial demography estimates. However, it is widely reported that Southeastern Africa bears over half the global burden of HIV, meaning that estimates used in analysis fit with the literature and disproportionate recruitment to RCTs stands even given a wide margin of error [8,35].

Conclusion

Non-white, female PLWH are substantially underrepresented in RCTs for novel ART. Safety data for these groups are insufficient or delayed. The present study indicates that changes to RCT recruitment practices are needed to gather an appropriate level of safety data for novel drugs. Regulatory RCTs should aim for at least 50% female and 50% non-white participants to provide sufficient safety data. Furthermore, detailed evaluation of regulatory RCT recruitment is indicated to assess underrecruitment of marginalised groups.

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Conflicts of interest

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