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Characteristics of HIV Controllers in the PHIA Surveys

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Master of Public Health

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An abstract of

A thesis submitted to the Faculty of the

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Abstract

Characteristics of HIV Controllers in the PHIA Surveys

By Sharon Bustrak

HIV controllers are a small group of exceptional individuals who innately suppress the virus without medication. The mechanisms of this control are varied and not completely understood, but controllers are generally found to be <1% of the HIV+ population. Using three definitions of controller, this descriptive analysis of 13 African Population-based HIV Impact Assessments suggests that controllers vary in prevalence between countries. Additionally, controllers have significantly higher CD4 counts, are on average older and, to some extent, are more likely to be female than their untreated, unsuppressed counterparts.

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Contents

Introduction:

Controllers of HIV are rare individuals who are able to suppress viral replication without the assistance of medication. Definitions of controllers vary, frequently using a composite of measures such as viral load levels, CD4 counts, and the amount of time viral or immunological control is maintained[1]. Viral load, the amount of the HIV virus in the body as measured by copies per milliliter, is an important indicator of the extent to which HIV has invaded the body. Higher levels are associated with poorer health outcomes and progression to AIDS[2]. Higher CD4 counts signify retention of immunological strength, with non-HIV infected individuals generally falling in the 500-1,600 cells/mm3 range[3]. Not all definitions of controllers use a time element, and those that do vary from 6 months to over ten years[1]. Elite controllers (ECs), the most stringent definition of controller, are generally described as individuals proven to have multiple viral load readings below 50 copies/mL for at least one year in the absence of antiretroviral medications [1,4]. However, many other definitions of controllers are found in the literature, sometimes referred to as viremic, immunologic, or simply HIV controllers[1].

Although ECs are generally thought to comprise less than 1% of HIV+ individuals, there is variation in prevalence between cohorts and countries [5]. For example, Kiros et al. examined two large HIV+ cohorts of Ethiopian patients, one in Ethiopia and one in Israel [6]. They found the prevalence of ECs (defined as ART-naïve individuals with undetectable viral load and stable CD4 counts > 500 copies/mL) to be 0.16% in Ethiopia and 0.6% in Israel. Using a similar viral load cut off but no CD4 consideration, mass screenings in Kinshasa, Democratic Republic of Congo found a higher-than-expected 2.7-4.3% prevalence of potential controllers [5]. Using a 2000 copies cut off, a West African study described 1.8% of participants who maintained viral control

after 30 months[7]. It is likely that some portion of this variation is attributable to use of different definitions of controlling, as well as measurement and methodological variation.

Clinical expression of both viremic and immunological control is diverse. Controlling does tend to be time limited, with most ECs experiencing loss of control in under 10 years [4]. However, Borrell et. Al (2021) found that 16.9% of a cohort of 59 controllers followed for a median of 17 years survived and maintained both viremic and immunological control [8]. Controllers also vary across other metrics. Post-treatment controllers are a subset who, after initiating and then discontinuing ARTs, are then able to independently control their viral levels for varying periods of time [9]. Additionally, other individuals may maintain healthy levels of CD4 cells with what Gaardbo et al. described as an immune homeostasis, despite also having higher viral loads than ECs[10,11].

Elite controllers often fall into the "undetectable" viral load category. That is, their viral load is so low it is not captured on the test used to measure it. Different tests measure to different thresholds, meaning this definition can functionally vary depending on the test used. It has been repeatedly proven that those who reach undetectable status (whether via consistent medication use or other paths) are unable to transmit HIV to others [12]. ECs are therefore epidemiologically important in that they do not sexually pass along the infection while they maintain their EC status.

The mechanisms by which individuals suppress the virus are complex and not completely understood. There are likely genetic, immunological, and virological factors, all of which may vary from controller to controller[11]. One value of studying these individuals and their many methods of control is the hope of a replicable model for an HIV cure. Turk et. Al (2022) report

an extreme case of an elite controller who, after over 8 years of living with HIV-1, has functionally eliminated the virus from their body [13]. While most controllers do not attain this outcome, studying these individuals can help researchers understand the potential of the human body to fight HIV.

In this paper we describe the prevalence of controllers in African countries severely affected by the HIV epidemic using data from the Population-based HIV Impact Assessments (PHIA) [14]. We examine three categories of controllers based on the Joint United Nations Programme on HIV and AIDS (UNAIDS) definition of viral suppression at <1000 copies/mL [15], the United States' Centers for Disease Control and Prevention (CDC) <200 copies/mL measure of viral suppression [15], and the definition of elite controllers generally found in the literature: <50 copies/mL [16]. Additionally, we assess differences in controller status by age and gender within and across countries, as well as differences between controllers and untreated non-controllers.

Methods:

PHIA surveys are nationally representative household-based surveys focused on countries heavily impacted by HIV. These surveys are collaborations by a country's Ministry of Health, the United States President's Emergency Plan for AIDS Relief (PEPFAR), CDC, and in some cases implementing partners such as ICAP at Columbia University and the University of Maryland-Baltimore [14]. These cross-sectional surveys include household and individual interviews and laboratory testing. Since 2014, surveys have been conducted in 16 countries. Some countries have had multiple rounds of data collection. This analysis describes HIV controllers based on data from publicly available PHIA surveys in 13 countries. Participants included in this analysis were those with all laboratory testing results available and were aged

15-80. The complete list of countries included can be found in Table 1. Years of data collection spanned 2015-2019.

Table 1. Description of PHIA participants by country. Proportions are weighted using PHIA blood weights. Counts are not weighted. Participants without weight data (n=4037) have been excluded.

Country	Study Population	Female (%)	HIV Prevalence (%)	HIV + Female (%)	Mean Age (range 15-80)	Year of Data Collection	Missing HIV Status
Combined	298795	170572	25303	17243	31.9	2015-2019	14270
Cameroon	27264	14818 (50.9)	980 (3.7)	690 (68.9)	31.9	2017-2018	NA
Cote d'Ivoire	18927	9429 (48.6)	444 (2.8)	304 (68.7)	31.8	2017-2018	1114
Eswatini	11673	6769 (54.4)	3003 (27.0)	2031 (65.5)	33.8	2016-2017	739
Ethiopia	20170	12158 (50.1)	614 (3.0)	461 (67.9)	31	2017-2018	NA
Kenya	30384	17476 (50.8)	1516 (4.9)	1095 (68.5)	31.6	2017-2018	2639
Lesotho	12887	7526 (49.9)	3199 (25.6)	2178 (59.3)	31.6	2016-2017	1205
Malawi	19652	11368 (51.6)	2227 (10.6)	1512 (64.5)	30.9	2015-2016	2465
Namibia	18796	10525 (51.9)	2446 (12.6)	1693 (64.6)	32.4	2017	NA
Rwanda	30715	16894 (52.1)	934 (3)	632 (64.4%)	32.1	2018-2019	NA
Tanzania	33004	18572 (51.3)	1831 (4.9)	1267 (66.2)	33.8	2016-2017	1425
Uganda	29383	16839 (52.6)	1772 (6.3)	1202 (64.4)	30	2016-2017	359
Zambia	21280	12109 (51.0)	2467 (12.0)	1688 (62.3)	29.9	2016	2165
Zimbabwe	24660	14454 (52.6)	3507 (13.6)	2285 (59.2)	34.3	2015-2016	2159

Due to the varying case definitions found in the literature [1,4], three different definitions of controllers were examined. Controllers were defined as HIV positive individuals not on ART with a viral load reading of <1000 copies/mL, < 200 copies/mL, or < 50 copies/mL respectively. The cross-sectional nature of the data required controllers be defined based on one viral load reading. The "art" variable was used to determine if a participant was or was not on ART. Those established to not be on ART are defined in the PHIA codebook as people living with HIV that were 1) aware or unaware of their status, without detectable ARVs and self-reported not on ART, or 2) aware of their status but missing ARV testing data and self-reported not on ART.

Table 2 describes controllers as weighted proportions of the HIV+ population from the surveys, and Table 3 describes them as weighted proportions of the untreated, HIV+ population.

As discussed by Patel et al., quality laboratory testing is a keystone of the PHIA surveys [16]. Whole blood specimens were collected from participants and subjected to multiple tests. Some tests, such as rapid HIV and Pima CD4 tests, were performed at point of care, after which further samples were transported within 12 hours to previously established satellite laboratories. These laboratories were required to have specific equipment and abilities and were assessed for readiness prior to data collection. Further processing, including confirmatory HIV testing, was performed at the satellite facilities. Plasma and dried blood spots were sent on to central laboratories where viral load testing was completed. Dried blood spots were sent to the University of Cape Town in South Africa for ARV analysis.

All analyses were performed using R Statistical Software (v4.2.2; R Core Team 2022) using the survey and tableone packages. Characteristics examined were age categories (15-30, 31-45, >45), sex, and CD4 count categories (<200, >=200). Jackknife weights were applied to create weighted proportions reflective of the general population in each respective country. Participants who did not have viral load or blood weight data were excluded from the analysis. Chi-square tests were performed for age category, sex, and CD4 category comparing controllers to HIV+, untreated participants who had unsuppressed viral loads. Participants who did not have data for the relevant variables were excluded from the chi-square tests.

Subsets of people living with HIV that met the inclusion criteria from each country were also pooled for a multi-country analysis. The previously mentioned descriptive analyses were conducted (Table 4), along with an examination using continuous age and CD4 count. Logistic

regression was used to examine the relationships between controller status, age, and gender at each of the viral load cutoffs.

Results:

Between the 13 countries considered in this analysis, the PHIA surveys included 298,795 participants with the variables of interest. Of these, 25,303 were HIV positive. Using the criteria of HIV+, a viral load <1000 copies/mL, and not on ART, 718 participants were determined to be elite controllers of HIV. That number decreased to 449 when looking at those with <200 copies, and 354 when using the 50 copies criteria. Detailed breakdown by country can be found in Table 2.

Table 2. Number and weighted proportion of all HIV+ study participants that meet definition denoted by the column headers.

Country	Unmedicated - All HIV positive participants	Unmedicated & VL < 1000 n (weighted %)	Unmedicated & VL < 200 n (weighted %)	Unmedicated & VL < 50 n (weighted %)
Combined	6970 (33.5)	718 (3.3)	449 (2.2)	354 (1.8)
Cameroon	481 (48)	41 (3.4)	30 (2.4)	28 (2.3)
Cote d'Ivoire	236 (54)	38 (6.3)	34 (5.7)	29 (4.6)
Eswatini	628 (22.7)	73 (2.6)	37 (1.3)	24 (0.8)
Ethiopia	133 (23.1)	18 (3.6)	11 (2.4)	9 (2.0)
Kenya	345 (23.7)	44 (2.6)	24 (1.5)	20 (1.4)
Lesotho	758 (25.5)	78 (2.4)	43 (1.3)	32 (0.9)
Malawi	651 (29.7)	94 (4.2)	59 (3.0)	44 (2.4)
Namibia	372 (17.1)	32 (1.7)	15 (0.6)	10 (0.4)
Rwanda	166 (18.3)	21 (2.4)	15 (1.7)	10 (1.1)
Tanzania	755 (42.1)	63 (3.4)	29 (1.6)	20 (1.2)
Uganda	584 (34.4)	89 (4.8)	73 (3.9)	68 (3.5)
Zambia	857 (37.4)	71 (3.0)	51 (2.1)	41 (1.7)
Zimbabwe	1004 (31.8)	56 (1.6)	28 (0.9)	19 (0.7)

Denominator is the entire HIV+ population, n = 25303.
All participants in the numerator are not on ART.

When looking specifically at unmedicated HIV+ participants, the weighted proportion who fit into the 1000 copies controller category varied from 15.4% in Ethiopia to 5.2% in Zimbabwe. When looking at the 50 copies definition, the highest and lowest percentages were in Uganda and Zimbabwe, at 10.0% and 2.0% respectively. Using weights specifically created for multi-country PHIA analyses, the weighted proportion of controllers among all untreated, HIV+ participants was 9.9% at the 1000 copies definition and 5.4% at the 50 copies definition.

Table 3. Number and weighted proportion of untreated HIV+ individuals that meet controller definition denoted by the column headers.

Country	VL <1000 n (weighted %)	VL <200 n (weighted %)	VL <50 n (weighted %)
Combined	718/6970 (9.9)	449/6970 (6.5)	354/6970 (5.4)
Cameroon	41/481 (7.2)	30/481 (5.1)	28/481 (4.8)
Cot Chart Title	38/236 (11.7)	34/236 (10.5)	29/236 (8.4)
Eswatini	73/628 (11.6)	37/6258 (5.7)	24/628 (3.6)
Ethiopia	18/133 (15.4)	11/133 (10.4)	9/133 (8.5)
Kenya	44/345 (11.1)	24/345 (6.5)	20/345 (5.8)
Lesotho	78/758 (9.5)	43/758 (4.9)	32/758 (3.6)
Malawi	94/651 (14.3)	59/651 (10.0)	44/651 (8.0)
Namibia	32/372 (10.0)	15/372 (3.2)	10/372 (2.2)
Rwanda	21/166 (13.3)	15/166 (9.5)	10/166 (6.3)
Tanzania	63/755 (8.2)	29/755 (3.9)	20/755 (2.8)
Uganda	89/584 (13.8)	73/584 (10.9)	68/584 (10.0)
Zambia	71/857 (8.2)	51/857 (5.7)	41/857 (4.7)
Zimbabwe	56/1004 (5.2)	28/1004 (2.9)	19/1004 (2.0)

Denominator is the untreated HIV+ population, n = 6970.

Rwanda and Kenya did not collect CD4 data. Seven of the 11 remaining countries showed a significant difference in dichotomous CD4 category (less than 200 or greater than or equal to 200) between controllers and untreated non-controllers. Controllers were significantly more likely to have CD4 counts higher than 200. There was missingness in the CD4 measurements in

seven of the 11 countries who did collect CD4 counts, ranging from 23 missing in Malawi and Uganda, to one missing in Eswatini.

When comparing participants who fell under the 1000 copies cutoff to those who were unmedicated and unsuppressed, four of the 13 countries showed chi-square p-values <0.05 when looking at gender. In all four countries, controllers were more likely to be women. Three countries showed statistically significant differences in age categories. The controllers in these countries had a generally older distribution.

We also combined the subsets of untreated HIV+ participants from all 13 countries. When comparing the combined <1000 copies definition of controllers to the combined unsuppressed group, controllers appeared to be older, with nearly 10% more people in the 46 years or older age group (Table 4). Looking at age continuously, controllers had a mean age of 37.0 years compared to unsuppressed participants at 35.5 years. Controllers in the <1000 copies category were also more likely to be female, with a male-female distribution of 35.6%-64.4%. The unsuppressed group was 42.7% male and 57.3% female.

Controllers across all definitions were more likely to have higher CD4 counts. The mean count for those under the 1000 copies cutoff was 705.9, as compared to 413.4 among unsuppressed individuals. This is a difference in mean of 292.6 (p value <0.0001, 95% CI 262, 322).

We fit a model examining the likelihood of being a controller based on the 1000 copies/mL definition, considering sex and age. According to our results, controllers have 40% increased odds of being female as compared to non-controllers (OR 1.41; 95% confidence interval (CI) 1.11 to 1.76). Using this same model with the 200 or 50 copies definition of controller provides odds ratios of 1.17 (95% CI 0.9 to 1.5) and 1.05 (95% CI 0.78 to 1.40), respectively for gender.

The 200 and 50 copies definitions showed statistically significant results with age, both with ORs of 1.02 (95% CI 1.0 to 1.03).

Table 4. Multi-country description and comparison of age category, sex, and CD4 category for three definitions of controllers to unsuppressed, untreated comparison group

Combined (untreated = 6970)	Controller, VL <1000 copies n = 718	Controller, VL <200 copies n = 449	Controller, VL <50 copies n = 354	Unsuppressed, not on ART n = 6252 (comparison group)
Age group				
n (weighted %)				
15-30	266 (36.7)	154 (35.5)	120 (35.8)	2422 (38)
31-45	269 (36.3)	159 (33.8)	122 (31.6)	2710 (44.5)
46+	183 (27.0)	136 (30.7)	112 (32.6)	1120 (17.5)
Chi-square p-value	< 0.0001	< 0.0001	< 0.0001	
Sex				
n (weighted %)				
Male	225 (35.6)	154 (39.6)	130 (42.1)	2394 (42.7)
Female	493 (64.4)	295 (60.4)	224 (57.9)	3858 (57.3)
Chi-square p-value	0.0082	0.4174	0.9654	
CD4 category				
n (weighted %)				
<200	16 (2.5)	9 (2.3)	8 (2.5)	1092 (18.8)
>= 200	573 (97.5)	341 (97.7)	258 (97.5)	4693 (81.2)
Chi-square p-value	< 0.0001	< 0.0001	< 0.0001	
	(CD4 missing = 129)			(CD4 missing = 467)

Discussion:

We found that controllers of HIV are, as suggested in the literature, a heterogenous group of individuals [4,17]. Interestingly, this is true when comparing across definitions of controllers. In keeping with previous findings, those who are suppressed at <1000 copies/mL are more likely to be female than untreated HIV+ individuals who are unsuppressed [18]. Controllers are also more likely to be older and have higher CD4 counts than the non-controller comparison group.

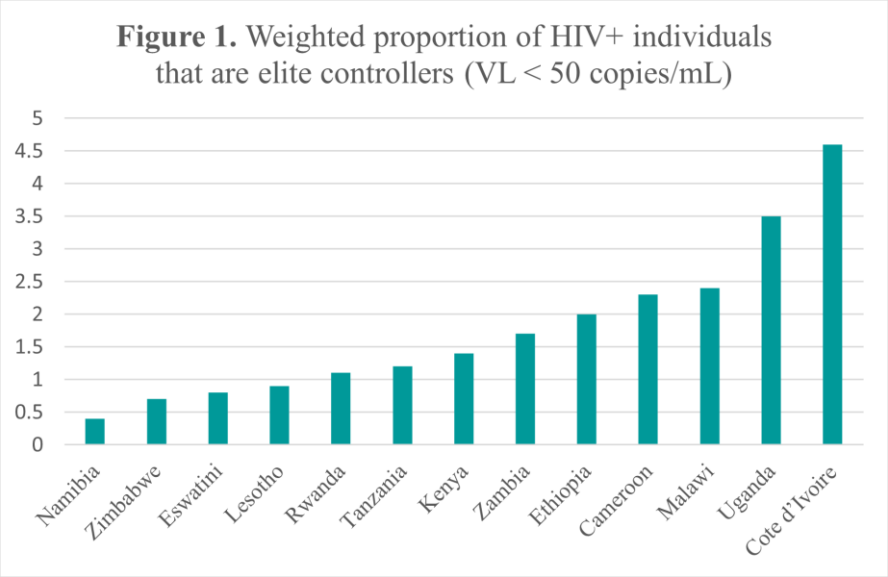
However, when looking at the 200 and 50 copies definitions, the odds of being female are no different between controllers and non-controllers. Mean age and CD4 count increased as viral load decreased. That is, elite controllers had higher mean ages and CD4 counts than any other group of untreated HIV+ individuals in this analysis.

Age distributions seemed to vary across countries. For example, in Cameroon more than 50% of controllers were in the 15- to 30-year-old age group, but more than 60% were above the age of 45 in Cote D'Ivoire. The relationship between age and controller status is not well established. Berg et al. found that both males and females with undetectable viral loads had younger median ages than their unsuppressed counterparts[5]. A prospective cohort study of female sex workers in Kenya, however, found that older age at infection was associated with controller status [19]. This could suggest that individuals infected at older ages could be more likely to be controllers, which could result in higher mean controller age. Controllers in the CASCADE cohort had varying mean ages at seroconversion depending on different definitions of controller used[20]. As such, our varied findings in terms of age distributions among controllers is unsurprising. That being said, investigation into possible reasons for between-country variation could be valuable.

Across all groups of controllers, CD4 counts were consistently and significantly higher than those of the comparison group. Interestingly, there is some evidence that CD4 counts have a generally lower baseline among African cohorts as compared to other groups, making controllers' higher numbers more notable[21] . Additionally, the mean CD4 count was higher for elite controllers (those with undetectable viral loads) than for the other controller definitions. There is a well-recognized association between controllers and higher CD4 counts, with many definitions including a stipulation that controllers have over a certain cutoff, such as 500[1]. This could suggest that our definitions in this context did a reasonable job of capturing individuals

who may in fact be true HIV controllers, despite the lack of longitudinal data. On a clinical level, higher CD4 counts suggest that controllers are likely to have healthier immune systems as compared to non-controllers.

Most articles about elite controllers (viral load below 50 copies/mL) state that they comprise <1% of the HIV+ population[6,17]. Some studies, however, find slightly higher prevalence. For example, the CASCADE cohort of over 25,000 HIV+ individuals from across multiple countries is thought to contain approximately 1.9% elite controllers when using a 50 copies cutoff[20]. When using a definition of <2000 copies over at least three viral load readings, the proportion of controllers in the same cohort increases to 5.5%[20]. Berg et al. estimate that the Democratic Republic of Congo may have higher than expected rates of controllers at 2.7-4.3%[5]. Although we found that controller prevalence varied across countries, the range was comparable to that found in the literature. The multi-country analysis showed a 1.8% weighted proportion of elite controllers, similar to the CASCADE findings. However, within individual countries, proportions varied from 0.7% in Zimbabwe to 4.6% in Cote d'Ivoire. The reasons for these differences between countries are unclear and warrant further exploration.



This analysis also compared controllers to their unsuppressed, untreated counterparts. Interestingly, another form of variation between countries was the distribution of each category of controller as a proportion of the untreated subpopulation. For example, 5.2% of untreated, HIV+ Zimbabweans fall under the 1000 copies definition of controller as compared to 2.0% using the 50 copies cut off. However, in Namibia the spread is from 10% to 2.2%. Again, the causes of these variations are likely multifactorial, but do have implications for HIV epidemic control goals. For example, if our estimates are accurate, as high as 15% of untreated HIV+ individuals in Ethiopia are virally suppressed without any kind of medication. Some of these individuals may also be unaware of their HIV status. 8.5% of untreated, HIV+ Ethiopians are undetectable, meaning they are also not passing the virus along in the community[12]. As such, despite controllers being a small proportion of the HIV+ population as a whole, they are an important consideration as we pursue epidemic control goals such as the 95-95-95[22].

One of the significant limitations of this analysis is the lack of longitudinal information. Controllers are often only defined as such after maintaining their low viral loads for at least one year[20]. As PHIA data are cross-sectional, it is unknown if those categorized as controllers may have been experiencing a low level of viremia due to their stage of natural disease progression, were post-treatment controllers, or were truly HIV controllers. Additionally, two countries, Rwanda and Kenya, did not provide CD4 data. There was also missingness in CD4 measures from many of the other countries, all of which may skew our results in regards to CD4 comparisons between controllers and non-controllers. Additionally, we restricted the analysis to the adult data set (ages 15-years-old and above), so any findings are not generalizable to younger children.

Another limitation is that the "art" variable used to classify controllers as unmedicated uses self-report when HIV status is known but information on bloodwork-based ART detection is missing. It has previously been shown that up to half of individuals in similar studies may incorrectly state they are not on medication despite ARTs being detected in their bloodwork[5]. This trend could result in overestimation of controllers using our definitions. However, the majority of participants did have ART bloodwork results available, so it is reasonable to assume that this type of misclassification in our analysis would not be extensive.

As discussed in the literature, there are many possible factors that contribute to an individual's ability to suppress HIV without medication[9,11,13]. Further investigations based on these data could include looking for any spatial clustering among controllers. Any such clusters could have multiple causes, such as transmission of specific, attenuated virus strains in an area [11] or genetic predispositions common in a community [17]. Although preliminary, it does seem controllers in some countries have different age distributions than those in other countries. This requires more granular examination, but could be at least partially attributable to local factors such as culture, various types of survival bias, or other unmeasured confounders.

With treatment guidelines advising all newly diagnosed patients begin ART immediately, identifying HIV controllers will become increasingly difficult. They will, however, continue to have improved prognoses and reduce transmission in communities where testing and treatment are scarce, as well as provide insight into possible long-term solutions to HIV infection.

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