Title
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Journal
AIDS, 30(16)

ISSN
0269-9370

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Publication Date
2016-10-23

DOI
10.1097/qad.0000000000001213

Peer reviewed

HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2017 October 23.

Published in final edited form as:

AIDS. 2016 October 23; 30(16): 2519–2528. doi:10.1097/QAD.0000000000001213.

Prevalence and Predictors of Low Muscle Mass in HIV/Viral Hepatitis Coinfection

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Abstract

Objective—Low muscle mass is associated with reduced survival in HIV, possibly mediated by systemic inflammation. Viral hepatitis coinfection can induce additional inflammation and hepatic dysfunction that may exacerbate low muscle mass. We determined the prevalence of and risk factors for low muscle mass in HIV/viral hepatitis coinfection.

Design & Methods—A cross-sectional study of participants in the Multicenter AIDS Cohort Study and Women's Interagency HIV Study with anthropometry performed after January 1, 2000. Viral hepatitis defined by positive hepatitis B virus surface antigen and/or hepatitis C virus RNA. Low muscle mass defined as $<10^{th}$ percentile of age- and sex-matched reference values for mid-upper arm circumference. Using multivariable logistic regression, we determined adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of: 1) the association of HIV/viral hepatitis coinfection with low muscle mass; and 2) factors associated with low muscle mass in coinfected

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ROLES OF AUTHORS: CG was responsible for study conception & design, data analyses and drafting of manuscript. TB, PT, CC, KF, and JK were involved in study design, reviewed data analyses and provided critical review of manuscript. PS was involved in study design, provided biostatistical support for data analyses and critically reviewed the manuscript. VLR was involved in study conception & design, participated in data analyses and provided critical review of manuscript.

Conflicts of Interest and Sources of Funding: The authors have no potential conflicts of interest to declare.

persons. Analyses adjusted for age, race, body mass index, alcohol use and injection drug use (also, nadir CD4 and HIV RNA where appropriate).

Results—Among 3,518 participants (164 HIV/viral hepatitis; 223 viral hepatitis alone; 1,070 HIV alone; 2,061 uninfected), HIV/viral hepatitis-coinfected persons had a 3.50-fold (95% CI, 1.51-8.09), 1.93-fold (1.17-3.20), and 2.65-fold (1.62-4.35) higher odds of low muscle mass than viral hepatitis-monoinfected, HIV-monoinfected, and uninfected persons, respectively. Lack of HIV RNA suppression (OR: 2.26 [1.10–4.63]) was the only factor associated with low muscle mass in coinfected persons.

Conclusions—HIV/viral hepatitis-coinfected persons have a higher likelihood of low muscle mass than those with viral hepatitis monoinfection, HIV monoinfection, or neither infection. HIV viremia is an important risk factor for low muscle mass among coinfected persons.

Keywords

low muscle mass; sarcopenia; viral hepatitis; HIV; MACS; WIHS

INTRODUCTION

Sarcopenia, defined as low muscle mass due to aging or other disease processes,[1-3] can have detrimental health consequences, including functional impairment, disability, and death.[4-6] Although sarcopenia occurs with normal aging, chronic infections can exert particularly profound changes in metabolic health and further exacerbate loss of muscle mass over time.

Sarcopenia is prevalent in HIV infection and has been independently associated with worse health outcomes, including progression to AIDS and reduced survival.[4,7-10] Mechanisms for muscle mass loss in HIV might include systemic chronic inflammation, increased resting energy expenditure, antiretroviral therapy (ART)-related fat redistribution and metabolic syndrome, and the impact of HIV-associated comborbidities.[7,8,11-14]

Viral hepatitis coinfection, present in up to 30% of HIV-infected patients,[15] may induce additional adverse nutritional and metabolic changes that exacerbate low muscle mass in HIV.[16-19] It has been previously shown that chronic hepatitis C virus (HCV) infection is associated with low muscle mass both prior to and after the development of cirrhosis.[20-22] Further, severe depletion of muscle mass and other signs of malnutrition are associated with increased mortality in chronic viral hepatitis.[21,22] Consequently, HIV/viral hepatitis-coinfected individuals might be at especially high risk of low muscle mass, and this condition may contribute to the adverse health outcomes and increased mortality observed in this population.[23,24] However, no studies have evaluated low muscle mass in HIV/viral hepatitis-coinfected patients.

To address existing knowledge gaps, we determined if HIV/viral hepatitis coinfection was associated with low muscle mass compared to HIV-monoinfected, viral hepatitis-monoinfected, and uninfected persons. We hypothesized that coinfected individuals would be at the highest risk of low muscle mass among these groups. We also identified risk factors associated with low muscle mass among coinfected persons.

METHODS

Study Design & Setting

We performed a cross-sectional study among participants in the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS). The MACS is composed of HIV-infected or at risk men who have sex with men at four US sites (Baltimore, Maryland/Washington, D.C.; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania) and has enrolled 7,317 men since 1984. The WIHS, initiated in 1994, enrolled 4,194 HIV-infected or at risk women from six US centers (Bronx, New York; Brooklyn, New York; Chicago, Illinois; Los Angeles, California; San Francisco, California; and Washington, DC) during three recruitment waves (1994-1995, 2001-2002, and 2011-2012). Participants in both cohorts attend semi-annual study visits, complete questionnaires on demographics, medical history, and risk behaviors, undergo physical examinations with anthropometry, and provide blood samples for serological testing. Details about the MACS and WIHS have been previously reported.[25-27] Study procedures performed at each participating MACS and WIHS site underwent regulatory review, and all participants provided informed consent. This study was approved by the University of Pennsylvania Institutional Review Board.

Study Participants

All participants in the MACS and WIHS were eligible for study inclusion if they were tested for HIV and viral hepatitis infections and had available anthropometric data. Viral hepatitis infection was defined by a positive hepatitis B virus (HBV) surface antigen (HBsAg) or detectable hepatitis C virus (HCV) RNA.

HIV/viral hepatitis-coinfected participants were included if they had: 1) positive HIV antibody, 2) received ART (defined as 3 or more antiretroviral drugs from at least 2 different antiretroviral classes, with exceptions made for combinations of three nucleotide reverse transcriptase inhibitors that include abacavir or tenofovir[28]) for ≥1 year after January 2000, 3) and had a positive HBsAg or HCV RNA. HIV-monoinfected participants had: 1) positive HIV antibody, 2) received ART for ≥1 year after January 2000, and 3) negative HBsAg and HCV antibody. Viral hepatitis-monoinfected patients had: 1) positive HBsAg or HCV RNA, and 2) negative HIV antibody and viral load. Uninfected participants had negative HIV antibody and viral load, negative HBsAg, and negative HCV antibody or undetectable HCV RNA.

We required all HIV-infected patients to have received ART for at least one year to avoid bias from differential treatment of HIV due to hepatitis or nutritional status and because substantial changes in body composition may occur in the first year after ART initiation.[10,29,30] We further required ART initiation after January 2000 to minimize exposure to nucleoside reverse transcriptase inhibitors, such as zidovudine (AZT), didanosine (DDI), or stavudine (D4T), that are associated with peripheral lipoatrophy.[31-33]

The index date was defined as the first study visit between 2000 and 2013 in which participants met eligibility criteria. Participants were excluded if they had a diagnosis of malignancy (except non-melanomatous skin cancers) or AIDS (CD4 <200 cells/μL) on or

prior to the index date, given well-established associations between these conditions and low muscle mass.[12,14,34-36]

Main Study Outcome

The primary study outcome was low muscle mass, defined by a mid-upper arm muscle circumference (MUAC) measurement below the 10th percentile for age- and sex-matched reference values derived from healthy US adults in the National Health and Nutritional Examination Survey, 1970-1974.[37] MUAC captures the loss of peripheral tissue stores of protein and muscle, has been used previously as a marker of low muscle mass in HIV and viral hepatitis populations,[8,20,38,39] and has been independently associated with increased mortality.[8,9,30,40] Use of anthropometric measurements to determine muscle mass is less likely to be subject to misclassification in chronic liver disease compared to other traditional measures of malnutrition, including body mass index (BMI) or serum markers (e.g. albumin, prealbumin).[41] Further, reference values were derived using data from NHANES participants from 1970-1974 because it was hypothesized that the rise in BMI over the last half-century has been driven primarily by increased adiposity, which would be associated with higher MUAC values that would not necessarily reflect an increase in muscle mass over this time period.[42-44]

To confirm the validity of MUAC as a measure of low muscle mass for this study, we evaluated the correlation between MUAC and fat-free mass determined by single-frequency bioelectrical impedance analysis (SF-BIA) among a subset of 1,360 participants who underwent simultaneous anthropometry and SF-BIA testing. MUAC measurements correlated well with fat-free mass determined by SF-BIA in this study (rho=0.71; $p<0.001$).

Data Collection

Self-reported demographic and clinical data collected on or prior to the index date included age, sex, race, ethnicity, education level, active alcohol use and injection drug use, and active and/or past use of AZT, DDI or D4T. BMI (kg/m^2) was obtained at physical examination.

Laboratory results collected at the same visit or the prior visit closest to the index date included: aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, and HIV viral load (copies/mL). Nadir CD4 cell count, defined as the lowest recorded CD4 prior to ART initiation, was also collected.

Two non-invasive laboratory measures of liver fibrosis, the AST-to-platelet ratio index (APRI) and the Fibrosis-4 (FIB-4) scores, were calculated.[45-47] APRI was determined as: ([AST [U/L]/upper limit of normal of AST]*100/platelet count [10^9 cells/L]; AST upper limit of normal=40 U/L).[47] An APRI score >2.0 has been shown to accurately identify cirrhosis (defined as METAVIR stage F4 or Ishak fibrosis score >5), while APRI <0.5 indicates absent or minimal fibrosis.[47] FIB-4 was calculated as: (age [years] * AST [U/L])/((platelet count [10^9 cells/L] * (ALT [U/L])$^{1/2}$). A FIB-4 score >3.25 identifies advanced hepatic fibrosis/cirrhosis, while scores <1.45 indicate no or minimal fibrosis.[45,46]

Statistical Analyses

Patient characteristics were evaluated by HIV/viral hepatitis status. Differences between groups were assessed using Chi-squared tests for categorical data and Wilcoxon rank-sum tests for continuous data. We determined the prevalence and 95% confidence intervals (CIs) of low muscle mass by HIV/viral hepatitis status. Results were stratified by HIV suppression status (HIV RNA <400 copies/mL) among HIV-infected patients.

Multivariable logistic regression was used to determine the adjusted odds ratios (OR) with 95% CIs of low muscle mass in HIV/viral hepatitis-coinfected patients compared to those with viral hepatitis alone, HIV alone, and uninfected persons, controlling for confounding variables in each comparison. Demographic and clinical variables were evaluated as potential confounders. Confounders remained in the model if the unadjusted OR changed by at least 10% after adjustment for the candidate factor or if a variable was considered *a priori* to be clinically important. We assessed if there were differential relationships between HIV/viral hepatitis infection and low muscle mass by sex, but observed no statistical interaction between infection status and sex. To evaluate associations between viral hepatitis and low muscle mass in the absence of cirrhosis, we repeated analyses excluding patients with APRI >2.0. In a sensitivity analysis, we evaluated the association between viral hepatitis and low muscle mass after controlling for active and/or past use of ARTs implicated in lipodystrophy (i.e. AZT, DDI and D4T). Analyses were also stratified by type of viral hepatitis infection in exploratory analyses. To isolate the effect of HIV RNA on the relationship between viral hepatitis coinfection and low muscle mass, analyses were repeated among HIV-infected persons stratified by HIV suppression.

Multivariable logistic regression was then used to evaluate risk factors for low muscle mass in coinfected patients. Hypothesized risk factors included active alcohol consumption, active injection drug use, lower nadir CD4 count, lack of HIV RNA suppression, and advanced liver disease (APRI >2.0; FIB-4 >3.25).

To address the potential bias of missing data, multiple imputation by chained equations was used to perform 20 imputations with all variables and the main study outcome included in the model.[48] Results were combined across the 20 datasets to arrive at the usual imputation CIs that accounted for within- and across-dataset variances.[49]

RESULTS

Among 11,511 participants enrolled in the MACS (n=7,317) and WIHS (n=4,194), 7,993 did not meet inclusion criteria (Figure 1). The final sample included 3,518 participants from the MACS (n=1,948) and WIHS (n=1,570), of whom 164 (5%) were HIV/viral hepatitis-coinfected, 223 (6%) were viral hepatitis-monoinfected, 1,070 (30%) were HIV-monoinfected, and 2,061 (59%) were uninfected. Chronic HCV accounted for the majority of viral hepatitis infections in the coinfected (n=124 [76%]) and viral hepatitis-monoinfected (n=189 [85%]) groups.

The characteristics of the patients are reported in Table 1. HIV/viral hepatitis-coinfected participants were more commonly non-Hispanic black and less educated, compared to all

other participants. Uninfected participants had the highest proportion of active alcohol users, while injection drug use and diabetes mellitus were most prevalent among those with viral hepatitis monoinfection. Nadir CD4 count and HIV RNA levels were similar between the HIV/viral hepatitis-coinfected and HIV-monoinfected groups, although fewer coinfected individuals achieved HIV RNA levels <400 copies/mL. Median BMI, waist circumference, and MUAC measurements were lower in the coinfected than all other groups (Table 1; p<0.001 for all comparisons).

The prevalence of low muscle mass was substantially higher in coinfected persons (n=45/164 [27%]) compared to those with viral hepatitis alone (n=23/223 [10%]), HIV alone (n=132/1,070 [12%]), and neither infection (n=198/2,061 [10%]) (p<0.001 for all; Table 1). Further, coinfected persons without HIV suppression (n=24/64 [38%]) had a higher prevalence of low muscle mass than those with HIV suppression (n=21/100 [21%]; p=0.021), whereas the prevalence of low muscle mass did not differ by HIV suppression status in the HIV-monoinfected group (n=32/294 [11%] without HIV suppression vs n=100/769 [13%] with HIV suppression; p=0.349).

After adjustment for age, sex, race/ethnicity, BMI, active alcohol consumption, and injection drug use (as well as nadir CD4 count and HIV RNA level in comparisons between coinfected and HIV-monoinfected), having HIV/viral hepatitis coinfection was strongly associated with low muscle mass compared to HIV alone (OR, 1.93 [95% CI, 1.17-3.20]), viral hepatitis alone (OR, 3.50 [95% CI, 1.51-8.09]), or neither infection (OR, 2.65 [95% CI, 1.62-4.35]) (Figure 2). Results were similar after exclusion of patients with cirrhosis by APRI (Figure 2). There was no statistical interaction between sex and infection status in any of our analyses (p>0.10 for all). After controlling for any historical use of AZT, DDI or D4T, HIV/viral hepatitis-coinfected participants still had increased odds of low MUAC when compared to uninfected (OR 1.90; 95% CI, 1.00-3.63), HIV-monoinfected (OR 1.80; 95% CI, 1.08-3.01), and viral hepatitis-monoinfected (OR 1.79; 95% CI, 0.40-8.14) persons. In exploratory analyses, we found similar results when viral hepatitis infection was restricted to those with HCV infection. There were too few participants with HBV infection to perform separate analyses in this group.

Specifically among HIV-infected patients, we assessed the impact of HIV RNA on the relationship between viral hepatitis coinfection and low muscle mass. Among patients without HIV RNA suppression, HIV/viral hepatitis coinfection was strongly associated with low muscle mass (OR, 3.24 [95% CI, 1.36-7.74]) when compared to HIV-monoinfected persons. However, among those with suppressed HIV, HIV/viral hepatitis coinfection was no longer associated with low muscle mass when compared to HIV monoinfection (OR, 1.31 [95% CI, 0.66-2.58]).

Among coinfected patients, absence of HIV suppression was the only risk factor for low muscle mass (Table 2). Nadir CD4 count, active alcohol consumption, active injection drug use, and non-invasive assessment of liver fibrosis were not associated with low muscle mass. Results were similar when FIB-4 was analyzed within models instead of APRI (Supplementary Table 1).

DISCUSSION

In this study, low muscle mass was significantly more common in HIV/viral hepatitis-coinfected persons compared to HIV-monoinfected, viral hepatitis-monoinfected, and uninfected persons. This finding persisted after adjustment for use of NRTIs associated with lipoatrophy among HIV-infected persons and after exclusion of those with cirrhosis as determined by APRI. Detectable HIV viremia was the main risk factor for low muscle mass in the coinfected group, suggesting there may be detrimental synergistic activity between viral hepatitis infection and uncontrolled HIV on muscle mass.

There are several potential mechanisms by which HIV/viral hepatitis coinfection could contribute to low muscle mass. A chronically heightened inflammatory state, driven by lack of HIV virologic control,[13,50] might impose greater metabolic demands on the body that, if unmet, could lead to muscle atrophy.[51] Direct liver injury exacerbated by HIV infection may impair cellular processes such as glycogenesis, gluconeogenesis, and protein synthesis, thereby promoting low muscle mass.[52-56] HIV can infect hepatic stellate cells and promote fibrogenesis.[57,58] Indeed, HIV viremia in HIV/HCV-coinfected patients has been associated with more rapid fibrosis progression compared to HCV-monoinfected and HIV/HCV-coinfected patients with undetectable HIV RNA.[57,59] In addition, chronic viral hepatitis could contribute to insulin resistance and the development of metabolic syndrome that already occurs in HIV-infected persons on ART, ultimately leading to steatohepatitis and further alterations in body composition.[60,61] Finally, HIV and viral hepatitis infections are associated with alcohol and other substance abuse,[62,63] which may contribute independently to low muscle mass in these individuals.

Persistent HIV viremia, likely mediated by ART non-adherence, was the only identifiable risk factor for low muscle mass for coinfected individuals. Absence of HIV suppression may also conceivably be a surrogate marker of social determinants, such as socioeconomic instability or food insecurity, that are more directly linked to low muscle mass. Alternatively, those with an inability to achieve HIV virologic suppression may harbor HIV strains with a higher replicative capacity or host-specific factors that also predispose to low muscle mass. However, if persistent HIV viremia actually was indirectly measuring these other social or host determinants, then low muscle mass would be expected to be more prevalent among HIV-monoinfected persons with uncontrolled HIV as well. Instead, the lack of associations between HIV viremia and low muscle mass in HIV monoinfection and between HIV/viral hepatitis coinfection and low muscle mass among those with HIV virologic suppression suggest that uncontrolled HIV and viral hepatitis infections actually may interact negatively to exacerbate the metabolic consequences of each.

Despite prior studies demonstrating a high prevalence of low muscle mass in cirrhosis, stage of hepatic fibrosis, determined by either APRI or FIB-4, was not associated with low muscle mass in HIV/viral hepatitis coinfection. While this may have been driven by a low prevalence of advanced liver disease in our study sample, it also suggests that the mechanisms underlying the development of low muscle mass in HIV/viral hepatitis coinfection may not be primarily mediated by loss of hepatic function. Systemic inflammation driven by uncontrolled HIV may be a critical factor contributing to low muscle

mass. Active alcohol and injection drug use were not determinants of low muscle mass, despite well-established relationships between these substances and malnutrition. [63-68] However, future studies should explore possible associations between low muscle mass and quantity of substance(s) used, since there may be threshold levels required before the detrimental effects of these substances on metabolic health are manifest.

These data build on prior work using the National Health and Nutrition Examination Study (NHANES,1999-2010) demonstrating that low muscle mass was more prevalent in chronic HCV infected persons compared to uninfected, healthy adults (13.8% vs 6.7%; odds ratio [OR], 2.22 [95% CI, 1.39-3.56]) in the U.S.[20] The prevalence of low muscle mass by anthropometry in HIV-monoinfected (12%) and viral hepatitis-monoinfected (10%) persons, respectively, was similar to that previously observed in HCV-monoinfected individuals (14%; p=0.481 and p=0.222). However, we observed a higher prevalence of low muscle mass among uninfected persons in our study (10% vs 6.7%; p<0.001), suggesting that the uninfected group here may not be reflective of the healthy, general population as captured in the contemporaneous NHANES population. This is likely driven by the selective enrollment of individuals at high risk for HIV in the MACS and WIHS cohorts, who may also have higher rates of substance use or other conditions that independently predispose to low muscle mass. Importantly, this may explain why the associations between low muscle mass and HIV or viral hepatitis monoinfection did not reach statistical significance when compared to uninfected persons. In addition, the magnitude of association between HIV/viral hepatitis coinfection and low muscle mass, as compared to uninfected persons in this study, may be an underestimate of the true impact of coinfection on low muscle mass.

This study has several potential limitations. Due to the cross-sectional design, we are unable to infer causality between HIV/viral hepatitis coinfection and low muscle mass. However, low muscle mass is not likely to lead to HIV or viral hepatitis infection independent of risk behaviors controlled for in the study. Although low muscle mass was defined using anthropometric measurements, we observed a strong correlation between MUAC and fat-free mass estimated by SF-BIA in a subgroup analysis, supporting its use. Although ascites can affect the validity of BIA measurements in chronic liver disease, the impact in this study was likely minimal due to the low proportion of participants with advanced liver disease (<2%). Incorporation of MUAC measurements alongside height and weight during routine clinic visits is highly feasible, without requiring highly specialized equipment, intensive training or invasive techniques, and may enable earlier detection of both low muscle mass and increased mortality risk in our patients.[40,69,70] Potential peripheral lipoatrophy from specific antiretrovirals could have confounded our results. However, this possibility was strongly mitigated by restricting our study to HIV infected persons initiating ART after January 2000 and by controlling for residual confounding from active and/or past use of implicated drugs. Triceps skinfold thickness and handgrip strength measurements were not available in this study, preventing us from using mid-arm muscle circumference or handgrip strength as complementary assessments of low muscle mass. However, these measurements could be feasibly obtained in the future and may enhance the clinical evaluation of low muscle mass. Lastly, there may be other factors, including physical activity indices and other medical or psychiatric comorbidities, that were not completely ascertained in this study

which may mediate the development of low muscle mass in HIV and viral hepatitis coinfection and should be explored in future studies.

In summary, HIV/viral hepatitis coinfection was associated with a substantially higher prevalence of low muscle mass compared to HIV monoinfection, HCV monoinfection and uninfected but at risk persons, even prior to the development of advanced liver disease. Absence of HIV suppression was a key risk factor for this outcome among coinfected patients. Future studies are needed to gain insight into the mechanisms underpinning the development of low muscle mass and further assess the impact of low muscle mass on disease progression and overall survival in HIV/viral hepatitis coinfection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This work was supported by the NIH/NIAID (research grants F32-AI120363 to CG; K24-AI108516 to PCT; and, R01-AI120733, K24-AI120834, and R01-AI093520 to TTB). CG and VLR were involved in study design, data analyses and manuscript preparation. TTB, CC, KAF, JK, PS and PCT provided critical review of data analyses and the manuscript. All authors approved the final version of the manuscript as submitted.

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH).

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This work was supported by the NIH/NIAID (research grants F32-AI120363 to CG; K24-AI108516 to PCT; and, R01-AI120733, K24-AI120834, and R01-AI093520 to TTB).

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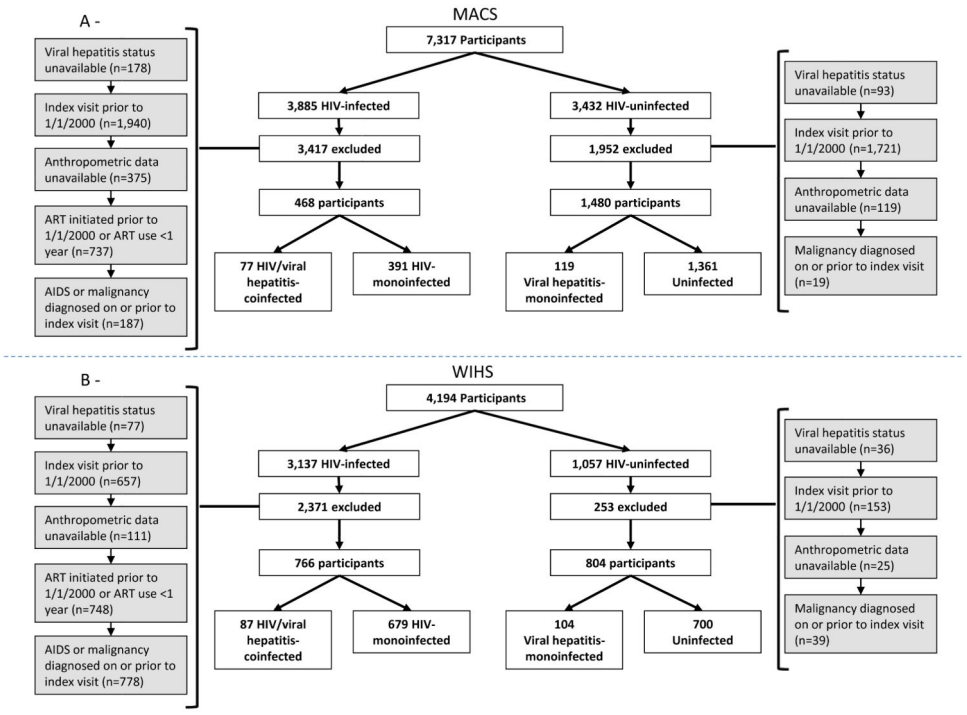

Figure 1.

Selection of HIV/viral hepatitis-coinfected, HIV-monoinfected, viral hepatitis-monoinfected, and uninfected participants from the Multicenter AIDS Cohort (MACS) and Women's Interagency HIV Study (WIHS) for inclusion in the study.

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; HIV, human immunodeficiency virus; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study

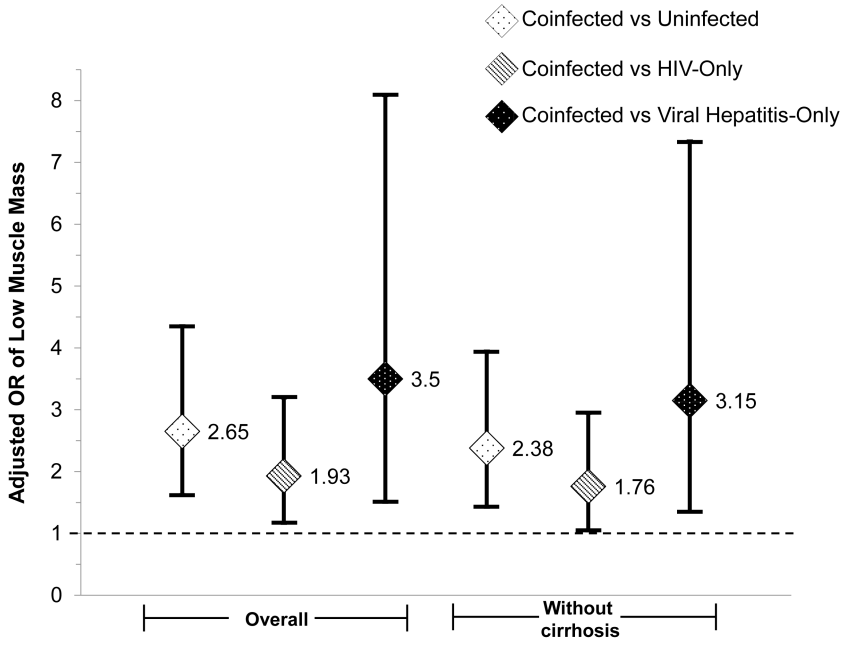

Figure 2.

Association between HIV/viral hepatitis-coinfected participants and low muscle mass, as compared to HIV-monoinfected, viral hepatitis-monoinfected and uninfected persons.

* All models adjusted for age, sex, race/ethnicity, body mass index, active alcohol use, and active injection drug use. Model comparing HIV/viral hepatitis coinfected to HIV monoinfected patients was additionally adjusted for HIV viral load and nadir CD4 count.

Table 1

Characteristics of HIV/viral hepatitis-coinfected, HIV-monoinfected, viral hepatitis-monoinfected, and uninfected participants at the index visit in the Multicenter AIDS Cohort and Women's Interagency HIV Study.

Characteristic	HIV/Viral Hepatitis Coinfected (n=164)	HIV Monoinfected (n=1,070)	Viral Hepatitis Monoinfected (n=223)	Uninfected (n=2,061)	Coinfected vs. HIV	P-value Coinfected vs. Viral Hepatitis	Coinfected vs. Uninfected
Median age, years (IQR)	42 (38 – 47)	38 (32 – 45)	45 (40 – 50)	42 (33 – 50)	<0.001	0.005	0.316
Male, n (%)	77 (47%)	391 (36%)	119 (53%)	1,361 (66%)	0.011	0.212	<0.001
Race, n (%)							
White	34 (21%)	403 (38%)	57 (26%)	1,154 (56%)	<0.001	0.011	<0.001
Black	123 (75%)	539 (50%)	140 (63%)	740 (36%)			
Other	7 (4%)	128 (12%)	26 (12%)	167 (8%)			
Hispanic, n (%)	27 (17%)	298 (28%)	31 (14%)	289 (14%)	0.002	0.485	0.389
Highest education level, n (%)							
<12th grade	63 (38%)	296 (28%)	66 (30%)	297 (15%)	0.005	0.069	<0.001
≥12th grade	101 (62%)	773 (72%)	157 (70%)	1,751 (85%)			
Active alcohol use, n (%)	88 (54%)	614 (58%)	150 (68%)	1,568 (77%)	0.345	0.005	<0.001
Active injection drug use, n (%)	27 (17%)	12 (1%)	71 (32%)	46 (2%)	<0.001	0.001	<0.001
Median nadir CD4, cells/uL (IQR)	278 (164 – 412)	283 (176 – 415)	--	--	0.602	--	--
Median HIV RNA, log_{10} copies/mL (IQR)	4.4 (2.3 – 5.5)	4.4 (1.7 – 4.9)	--	--	0.119	--	--
HIV RNA <400 copies/mL, n (%)	100 (61%)	769 (72%)	--	--	0.003	--	--
Viral hepatitis status, n (%)							
HCV RNA-positive	124 (76%)	--	189 (85%)	--	--	0.063	--
HBsAg-positive	37 (23%)	--	32 (14%)	--	--		--
HCV RNA-positive & HBsAg-positive	3 (2%)	--	2 (1%)	--	--		--
Diabetes mellitus, n (%)	21 (14%)	100 (10%)	39 (21%)	171 (10%)	0.105	0.088	0.097
Median BMI, kg/m^2 (IQR)	24 (22 – 28)	26 (23 – 31)	27 (24 – 31)	26 (24 – 31)	<0.001	<0.001	<0.001
BMI (kg/m^2), n (%)							
<18.5	4 (2%)	18 (2%)	2 (1%)	24 (1%)	<0.001	<0.001	<0.001
18.5-24.99	85 (52%)	375 (35%)	77 (35%)	736 (36%)			
25-29.99	51 (31%)	335 (32%)	72 (33%)	697 (34%)			

Characteristic	HIV/Viral Hepatitis Coinfected (n=164)	HIV Monoinfected (n=1,070)	Viral Hepatitis Monoinfected (n=223)	Uninfected (n=2,061)	Coinfected vs. HIV	P-value Coinfected vs. Viral Hepatitis	Coinfected vs. Uninfected
≥30	22 (14%)	329 (31%)	69 (31%)	575 (28%)			
Median waist circumference, cm (IQR)	86 (78 – 95)	90 (81 – 101)	91 (83 – 103)	92 (83 – 102)	<0.001	<0.001	<0.001
Median mid-upper arm circumference, cm (IQR)	29 (26 – 33)	31 (28 – 35)	32 (28 – 35)	32 (29 – 35)	<0.001	<0.001	<0.001
Low muscle mass[a]	45 (27%)	132 (12%)	23 (10%)	198 (10%)	<0.001	<0.001	<0.001

Abbreviations: BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range

[a]Low muscle mass, determined by anthropometry, was defined as <10th percentile of age- and sex-matched reference values for mid-upper arm circumference

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Table 2

Risk factors for low muscle mass among HIV/viral hepatitis-coinfected participants.

Risk Factor	Unadjusted OR of Low Muscle Mass[a] (95% CI)	Adjusted[b] OR of Low Muscle Mass (95% CI)
Alcohol use		
No	Ref	Ref
Yes	1.55 (0.77-3.14)	1.56 (0.75-3.23)
Active injection drug use		
No	Ref	Ref
Yes	1.66 (0.69-3.96)	1.73 (0.70-4.31)
AST-to-Platelet Ratio Index		
< 0.5	Ref	Ref
0.5 – 2.0	0.93 (0.45-1.93)	0.87 (0.41-1.86)
> 2.0	2.68 (0.51-14.2)	3.17 (0.56-18.0)
Nadir CD4 count (per 50 cells/mm^3)	0.94 (0.85-1.04)	0.95 (0.86-1.05)
HIV RNA (copies/ml)		
<400 copies/ml	Ref	Ref
≥ 400 copies/ml	**2.26 (1.12-4.54)**	**2.26 (1.10-4.63)**

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio

[a] Low muscle mass, determined by anthropometry, was defined as <10th percentile of age- and sex-matched reference values for mid-upper arm circumference

[b] Multivariable model incorporated all potential risk factors of interest, including alcohol use, injection drug use, nadir CD4 count, HIV RNA and AST-to-Platelet Ratio Index.