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Article

Prevalence of Post-Acute COVID-19 Sequalae and Average Time to Diagnosis among Persons Living With HIV (Meta-Analysis and Meta-Regression)

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Abstract: Aims: The aims of this meta-analysis were to assess: the prevalence of Post-Acute COVID-19 sequalae in HIV positive patients; average time of diagnosis; and meta-regress for possible moderators of PACS. **Methods:** A standard search strategy was used in PubMed, and then later modified according to each specific database to get the best relevant results. These included Medline indexed journals; PubMed Central; NCBI Bookshelf and publishers' Web sites in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis statement. Search terms included "long COVID-19 or post-acute COVID-19 syndrome/sequalae", "persons living with HIV or HIV. The criteria for inclusion were published clinical articles reporting HIV in association with long COVID-19, further, the average time to an event of post-acute COVID-19 sequelae among primary infected patients with COVID-19. Random-effects model was used. Rank Correlation and Egger's tests were used to ascertain publication bias. Sub-group, sensitivity and meta-regression analysis were conducted. A 95% confidence intervals were presented and a p-value < 0.05 was considered statistically significant. Review Manager 5.4 and comprehensive meta-analysis version 4 (CMA V4) were used for the analysis. The review/trial was PROSPERO registered (CRD42022328509). **Results:** A total of 43 studies reported post-acute COVID-19 syndrome. Of those, five reported post-acute COVID-19 sequalae in PLHIV. Prevalence of post-acute COVID-19 sequalae was 43.1% (95% CI 20.5% to 68.9%) in persons living with HIV (PLWH). The average time to PACS diagnosis was 4 months at 64% [0.64 (95% CI 0.230, 0.913) (P < 0.0000), I^2= 93%] and at one year to PACS diagnosis was at 70 %, however with non-significant correlation (P > 0.05). On comorbidities, asthenia was associated with PACS at 17.6 % [0.176 (95% CI 0.067, 0.385) (P = 0.008), I^2= 86%] while fatigue at 82%, however not related with PACS event incidence (P < 0.05). Americas, Asian and European regions showed PACS events rates of 82%, 43% and 19 % respectively (P<0.05) relative to HIV infection. **Conclusion**: PACS prevalence in PLWH was 43% occurring at an average time of 4 months at 64% and 70 % at 12 months however non-significant with PACS. Asthenia was significantly associated with PACS at 17.6 % while fatigue at 82%, however not related with PACS event incidence. Americas recorded the highest PACS event rates in PLWH.

Keywords: post COVID-19 Sequelea; HIV; meta-analysis; covariates

Introduction

Long COVID-19 may be defined as patients who, four weeks after the diagnosis of SARSCov-2 infection, continue to have signs and symptoms not explainable by other causes[1]. Recent reports have described persistent symptoms extending beyond the period of initial illness or hospitalization. Anecdotes of different signs and symptoms occurring after acute infection have also arisen in the lay press[2]. Long COVID encompasses multiple adverse outcomes, with common new-onset conditions

including cardiovascular, thrombotic and cerebrovascular disease[3], type 2 diabetes[4], myalgic encephalomyelitis/chronic fatigue syndrome[5]. This post-acute infection represents a significant challenge for patients, physicians, and society because the causes, patient profile, and even symptom patterns remain difficult to characterize[6]. It may include memory loss, gastrointestinal (GI) distress, fatigue, anosmia, shortness of breath, and other symptoms. PASC has been associated with acute disease severity[7], further, it is suspected to be related to autoimmune factors[8], as well as unresolved viral fragments[9]. Post-COVID conditions are found more often in people who had severe COVID-19 illness, but anyone who has been infected with the virus that causes COVID-19 can experience post-COVID conditions, even people who had mild illness or no symptoms from COVID-19[10].

The COVID-19 pandemic has substantially affected the lives of people living with HIV (PLHIV), who frequently face multiple morbidities and may be at heightened risk for COVID-19 complications, with spillover effects on other aspects as equitable access to treatment and prevention[11–13]. Further, PACS has been established as a common phenomenon in PLWH[14].

There is a paramount importance in understanding the complexities of long COVID in general, further in immune compromising related comorbidities such as the current one on this study. The body of knowledge being developed to better understand post-COVID syndrome should be accustomed to the most vulnerable populations after mapping out the context of the phenomena among the general population. Studies of patients who have recovered from SARS-CoV-2 infection but have persistent symptoms have ranged widely in size, quality, and methodology, leading to confusion about the prevalence and types of persistent symptoms[15], a peculiar issue possibly in HIV infection that requires an updated information through valid and most recent data to inform any on-going clinical, rehabilitative and public health practice. SARS-CoV- 2 can produce short/long-term sequelae and the reports describing post-acute COVID-19 syndrome (PACS) in the general population are increasing, but comprehensive data are lacking in people living with HIV (PLWH). Therefore, this review aimed at assessing the prevalence and factors associated with PACS in our cohort of PLWH.

Methods

A standard search strategy was used in PubMed, and then later modified according to each specific database to get the best relevant results. These included MEDLINE indexed journals; PubMed Central; NCBI Bookshelf and publishers' Web sites. The language was restricted to English and the search dates were for studies conducted/published between June 2021 and August 2022. The basic search strategy was built based on the research question formulation (i.e., PICO or PICOS)[16]. They were constructed to include free-text terms (e.g., in the title and abstract) and any appropriate subject indexing (e.g., MeSH) expected to retrieve eligible studies, with the help of an expert in the review topic field or an information specialist. The summary of search terms was; long COVID-19; long COVID-19 syndrome; post-Corona Virus syndrome; Post-acute COVID-19 sequelae; Post-acute COVID-19 syndrome; Post-acute COVID-19 condition; HIV; HIV infection; HIV disease, etc. Because the study for this topic would be limited, the outcome term (long COVID-19) in the search term was not be included initially in order to capture more studies. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[17] was used. All identified article titles and abstracts were screened independently by two authors (JKM, JMN), with those meeting the inclusion criteria screened further by full text review. On occasions when it was not clear from the abstract if studies were of relevance, the full text of the article was reviewed. Unanimous consensus was met on the inclusion of proposed studies for full text review among the authors. Full text studies were further evaluated against the inclusion and exclusion criteria. The reference lists of included studies were reviewed to ensure no other relevant studies were overlooked.

Search terms and criteria for inclusion

Search terms included for PubMed was as follows: (long COVID-19; long COVID-19 syndrome; post-Corona Virus syndrome; Post-acute COVID-19 sequelae; Post-acute COVID-19 syndrome; Post-acute COVID-19 condition) AND ("the study" [Publication Type] OR "study as the topic" [MeSH

Terms] OR "study" AND HIV serostatus AND [All Fields]). A search limit for articles published from mid-2020 2021 applied. The criteria for inclusion were published research articles reporting: 1) the rate prevalence of post-acute COVID-19 syndrome (at admission or following admission) among PLHIV and the possible associated clinical parameters. Studies were excluded if they were case reports, review articles, conference abstracts, non-clinical studies, or were not available in the English language.

Data extraction

The included studies were evaluated for the authors, year of publication/ the study was conducted, title, where it was conducted, study design, time of diagnosis of post-acute COVID-19 sequalae (on admission or following admission with mean/ average time to diagnosis in months) and HIV infection relative to post-acute COVID-19 sequalae. A post-acute COVID-19 sequalae case was defined as the illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually within three months from the onset of COVID-19, with symptoms and effects that last for at least two months.

Outcome measures

The primary objectives were to estimate the prevalence of post-acute COVID-19 sequalae in PLWH as from mid-2020and average time of acquiring/being diagnosed with post-acute COVID-19 sequalae. Secondary objectives included meta-regressing for any possible and predetermined covariates to ascertain of any relationship with post-acute COVID-19 sequalae.

Quality assessment

Using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[18], all included publications were reviewed independently for potential risk of bias by two authors (JKM, JMN). The assessment tool uses 14 questions to enable allocation of a score to each article (poor, fair, or good). If there was disagreement regarding the scoring of a study, consensus was met after discussion among both assessors.

Statistical analysis

Simple descriptive analysis was performed for the five aims of the review. Heterogeneity among the studies was assessed using the chi-squared test and I^2, however due to suspected variation among the studies and associated heterogeneity random effects models were used for all meta analyses[19]. Post-acute COVID-19 events rates were estimated using random-effects model, the mortality associated with post-acute COVID-19 sequalae was statistically assessed using random effects models (DerSimonian and Laird)[20], and event rates (ER) were presented. Publication bias was assessed using Begg and Mazumdar Rank Correlation Test and the Egger's Test of the Intercept and a precision funnel plot was used to ascertain this the publication bias status. To account for any possible heterogeneity (I^2), sub-group and sensitivity analysis were conducted and in this, some analysis used fixed-effect model analysis, further to these, meta-regression analysis was run for specific pre-determined covariates. For each outcome variable, 95% confidence intervals (CIs) were presented. A p-value < 0.05 was considered statistically significant. This meta-analysis and meta-regression were conducted using comprehensive meta-analysis version 4 (CMA v4).

Results

A list of the five studies [14,22–25] detailing PACS in PLWH that met the inclusion criteria are illustrated below in *Table 1.*
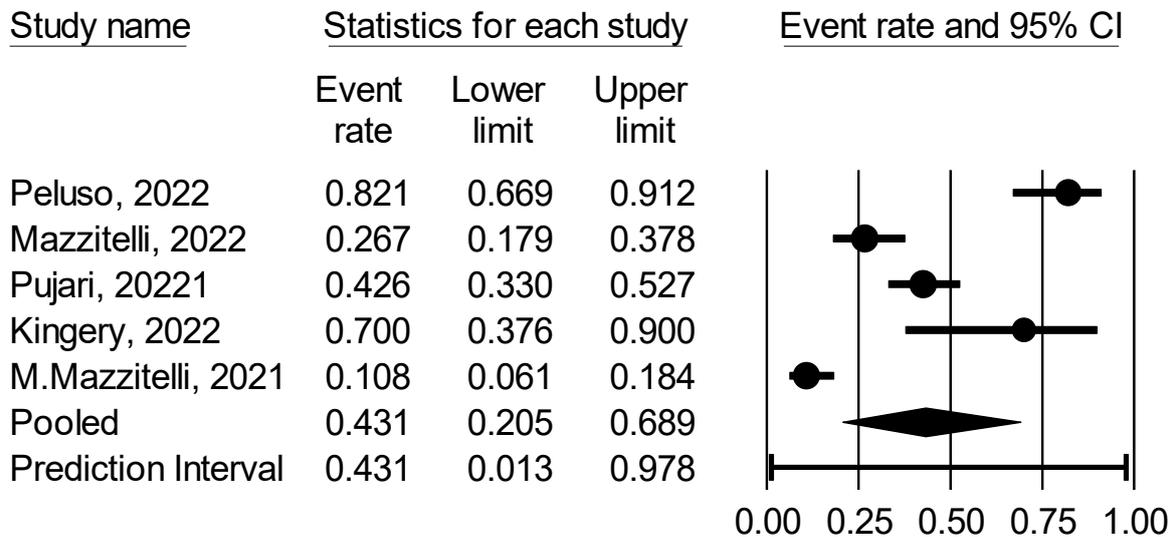
Table 1. Summery of the studies used in the analysis.

	Study/Author	Region	Study Design	Study Setting	Average time to PACS diagnosis (in months)
1.	Peluso, 2022	USA	Prospective	Single	4
2.	Mazzitelli, 2022	Europe	Prospective	Multicenter	6
3.	Pujari, 2022	Asia	Prospective	Single	4
4.	Kingery, 2022	USA	Retrospective	Single	12
5.	Mazzitelli, 2022	Europe	Prospective	Single	1

Figure 1 PRISMA flow diagram showing studies identified and included in a systematic meta-analysis.
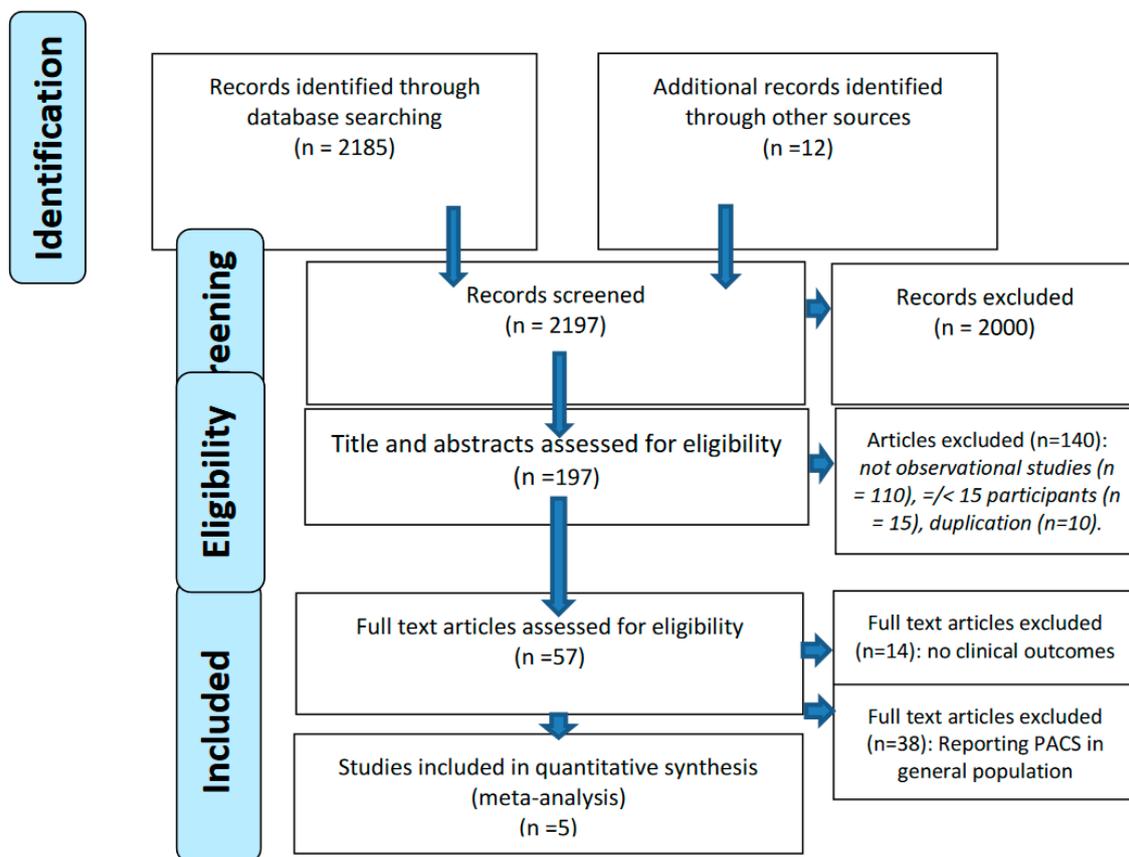
Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram for the studies identified and included in the review.

Post-acute COVID-19 sequalae event rate in PLHIV

From the analysis based on five studies detailing Post-acute COVID-19 sequalae in PLHIV (n= 320) [14,22–25], the prevalence ranged between 11% to 82% with the mean event rate at 43.1% (95% CI 20.5%, 68.9% [Heterogeneity: Tau² = 1.349; Chi² = 57.197, df = 4 (P = 0.0000); I² = 93%] (*Figure 2*).

Prevalence of post-acute COVID-19 sequalae in PLHIV

Study name	Statistics for each study			Event rate and 95% CI
	Event rate	Lower limit	Upper limit	
Peluso, 2022	0.821	0.669	0.912	
Mazzitelli, 2022	0.267	0.179	0.378	
Pujari, 20221	0.426	0.330	0.527	
Kingery, 2022	0.700	0.376	0.900	
M.Mazzitelli, 2021	0.108	0.061	0.184	
Pooled	0.431	0.205	0.689	
Prediction Interval	0.431	0.013	0.978	

Meta Analysis

Figure 2. Post-acute COVID-19 sequalae event rate in PLHIV.

The prediction interval in 95% of all the comparable populations fell between 0.013 to 0.978 demonstrating that, in some populations, the event rates of PACS is at one extreme as low as 1.3% and as high as 98%, this variation reflected differences in real proportions (*Figure 3*).
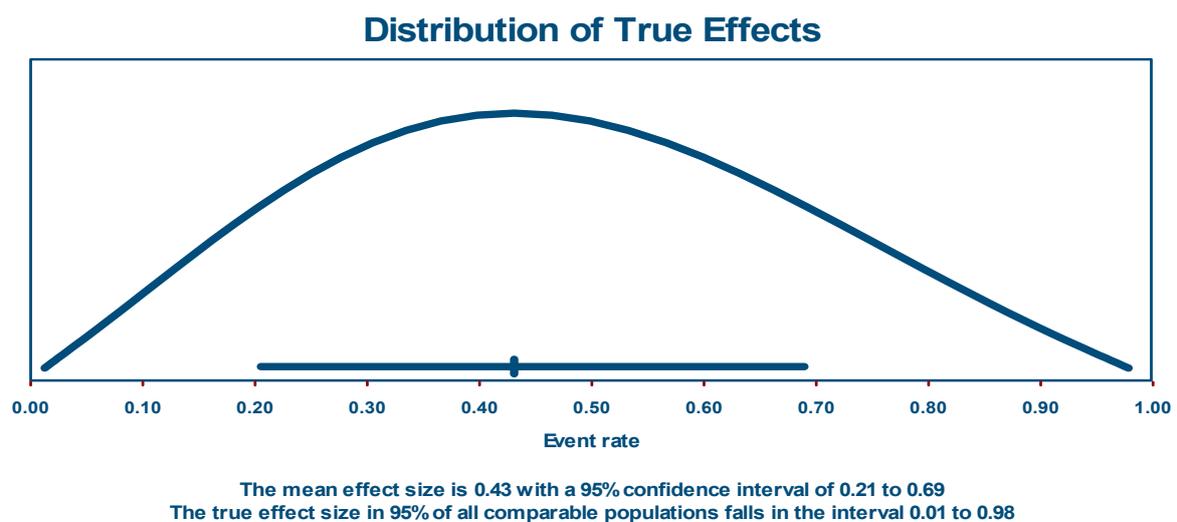
Distribution of True Effects

The mean effect size is 0.43 with a 95% confidence interval of 0.21 to 0.69
The true effect size in 95% of all comparable populations falls in the interval 0.01 to 0.98

Figure 3. Distribution of true effects on post-acute COVID-19 sequalae event rate in PLWH.

Begg and Mazumdar Rank Correlation Test (Kendall's tau b = 0.10000, P-value = 0.40325) and Egger's Test of the Intercept (Intercept = 3.26596, 95% CI (-13.66376, 20.19568), with t=0.61394, df=3. P-value = 0.29134, indicated an absence of publication bias (Figure 4).
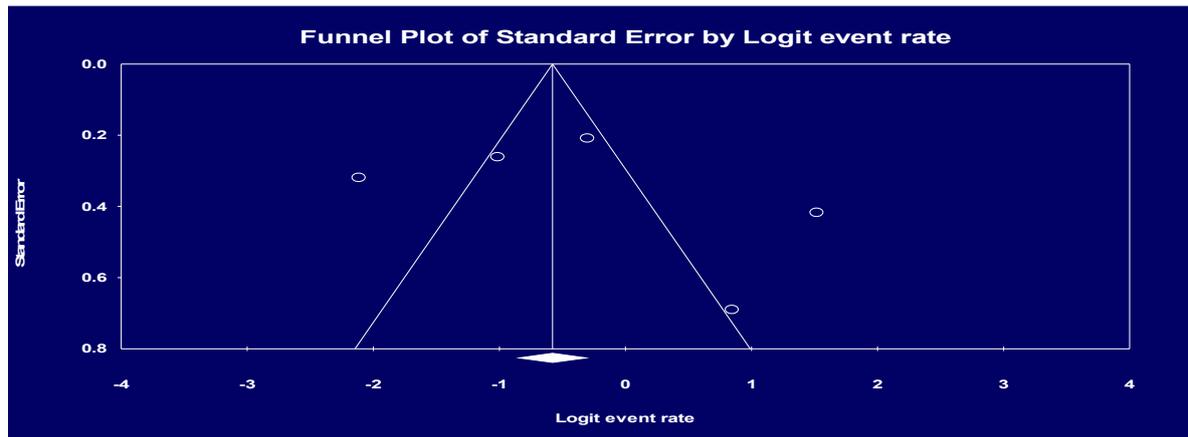
Figure 4. Funnel plot of publication bias.

A sensitivity analysis by removing one study with the highest event rate (82%)[22], the new mean event rate was 32 % (95% CI 15 %, 55%), a significant difference from the original 43.1 %. This showed that, the mean PACS event rate estimation was contributed differently by each study (p-value >.05) (Figure 5).

Post-acute COVID-19 sequalae in PLHIV

Study name	Statistics with study removed					Event rate (95% CI) with study removed
	Point	Lower limit	Upper limit	Z-Value	p-Value	
Peluso, 2022	0.319	0.153	0.549	-1.557	0.119	
Mazzitelli, 2022	0.485	0.178	0.804	-0.079	0.937	
Pujari, 20221	0.440	0.140	0.791	-0.300	0.765	
Kingery, 2022	0.377	0.157	0.663	-0.833	0.405	
M.Mazzitelli, 2021	0.545	0.301	0.769	0.344	0.731	
	0.431	0.205	0.689	-0.507	0.612	

Meta Analysis

Figure 5. A sensitivity analysis by removing one study on post-acute COVID-19 sequalae event rate in PLHIV.

Sub-group and meta-regression analysis

To account for the substantial heterogeneity, it deemed applicable to better understand whether and which study-level factors drove the measures of effect. This meta-regression analysis featured as per the objectives of this meta-analysis on the prevalence of Post-Acute COVID-19 sequalae in HIV positive patients and average time of PACS diagnosis.

PLWH (HIV positive patients) with only the five studies detailing HIV disease [14,22–25] relative to post COVID-19 syndrome, subgroup analysis showed that, average time of four (4) months to PACS diagnosis was associated with PACS event incidence at 64% [0.64 (95% CI 0.230, 0.913) (P < 0.0000), I^2= 93%], with random effects model. An average time of one year to PACS diagnosis was at 70 %, however it did not show any significance with PACS event (P > 0.05) (Fig 18). On the other hand, asthenia in PLHIV was the most associated comorbidity with PACS event at 17.6 % [0.176 (95% CI 0.067, 0.385) (P = 0.008), I^2= 86%]. Fatigue was at 82% in PLWH as shown by one study[22], however it was not related with PACS event incidence (P < 0.05). Sub-group analysis (fixed effect model) by region demonstrated higher PACS event rates in the United States of America relative to HIV infection, followed by Asian region and European region at 79%(P> 0.05), 43%(P>0.05) and 19 % respectively (P<0.05) (Table 2).

Table 2. Meta-analysis grid table on region of study sub-analysis.

Group	Number S	Point esti	Lower lim	Upper lim	Lower limit	Upper limit	Tau	TauSq	Q-value	df (Q)	P-value	I-squared
Fixed effect analysis												
Asia	1	0.425532	0.329825	0.527165					1.17E-15	0	1	0
Europe	2	0.189522	0.135961	0.257886					7.1319481	1	8.00E-03	85.97858562
USA	2	0.792452	0.65474	0.884892					0.6955181	1	0.404	0
Total within									7.8274662	2	2.00E-02	
Total between									49.369733	2	1.90E-11	
Overall	5	0.359412	0.301225	0.422051					57.197199	4	1.12E-11	93.00665057
Random effects analysis												
Asia	1	0.425532	0.168711	0.729991	3.92E-02	0.93072	0.626759041	0.392826896				
Europe	2	0.176121	7.58E-02	0.35769	1.68E-02	0.72831	0.626759041	0.392826896				
USA	2	0.778044	0.526539	0.917006	0.186062616	0.981736	0.626759041	0.392826896				

Discussion

This systematic review, meta-analysis and meta-regression sought to estimate the prevalence of post-acute COVID-19 sequalae in general population using the most recent data, which was done from 43 studies [7,26–70] detailing post-acute COVID-19 syndrome, of which, five reported post-acute COVID-19 sequalae in PLHIV and average time of acquiring/being diagnosed with post-acute COVID-19 sequalae. Secondary objectives included meta-regressing for any possible and predetermined covariates to ascertain of any relationship with post-acute COVID-19 sequalae.

Post-acute COVID-19 sequalae prevalence (event - rate) in PLHIV was 43.1%   similar to another primary study findings that, the prevalence of long-COVID was 43.6%[14] and significantly related with HIV infection as in case of a study that demonstrated that, HIV status strongly predicted the presence of PASC[22]. PLWH (HIV positive patients) developed signs and symptoms related to post COVID-19 syndrome at an average time of four (4) months, similar to a primary study that showed that, 4 months post COVID-19 infection, PLWH reported fatigue (42%), muscle pain (24%), concentration problems (42%), vision problems (21%) and trouble sleeping (34%)[22], which are common post-acute COVID-19 sequalae signs and symptoms. Asthenia and fatigue were seen as the most persistent symptoms. This is consistent with previous findings suggestive of brain involvement which brings about similar lethargic feelings[71].   Seemingly, although in non-HIV population, a study[72], concluded that, persistent symptoms after the first wave of COVID-19 in relation to SARS-CoV-2 serology and

experience of acute symptoms: A nested survey in a population-based cohort, similar to current findings on asthenia. Similar conclusion again that,

Recent studies further report that, people with HIV are more likely to experience 'long COVID' symptoms and to experience serious cardiovascular and metabolic disorders and cancers after being diagnosed with COVID-19[73]. Two US researchers involved in long COVID research say there is an urgent need to understand why people with HIV are more vulnerable to long COVID and to include them in clinical trials of potential long COVID treatments[73]. The perceived prevalence of PACS in PLHIV can also be explained by recent pre-print findings where HIV plays a role as a risk predictor of long COVID-19 symptoms along side other conditions with a conclusion that, underlying HIV infection was also independently associated with neurocognitive LC (OR = 2.5)[74].

A limitation of the current review was the defined inclusion criteria for a post-acute COVID-19 sequalae patient, presenting with either one or more suspected signs and symptoms depicting the syndrome. Limited number of studies (only five), seemed not sufficient enough however, these studies were retrieved from a review that consisted 43 studies categorizing PACS in general population.

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