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COVID-19 and HIV/AIDS: Effectiveness of ART in reducing mortality- A meta-analysis

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***Abstract*---**Background: Patients who are immune-compromised have a poorer outcome from most serious infections, but this may vary depending on the type of immune deficiency and the pathogens. This study is conducted to assess the effectiveness of ART in reducing mortality in HIV/AIDS patients suffering from COVID-19. Materials and Methods: Databases including PubMed, Medline and Scopus from

May 2021 to June 2021were searched for studies describing effectiveness of ART in reducing mortality among HIV/AIDS and COVID-19 co-infection patients. Quality assessment of the articles was done using CEBM checklist for different study designs.486 studies were identified and only 8 were of fair and good quality. Statistical analysis was done using STATA version 16 based on random effect model. Results: Out of total study participants, above 92.2% of PLWHA were on ART therapy. ART was associated with a higher effectiveness among HIV & SARS-CoV-2 infection (Effect Size 85.41; 95% CI; 78.35-92.48). Conclusion: Findings conclude that among HIV patients receiving Anti-Retroviral Therapy and infected by COVID-19 disease, the risk of severity and mortality is comparatively less. Further investigation into the effectiveness of ART among HIV/AIDS co-infection is warranted.

***Keywords*---**COVID-19, HIV, ART, SARS-Cov-2 and Coronavirus.

Introduction

The causative agent of coronavirus disease-19 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected millions of people worldwide since its first reports from Wuhan in China in early December 2019. COVID-19 has been spreading worldwide, and the outbreak was declared a pandemic by the World Health Organization on 12 March 2020.[1]

COVID-19 symptoms range from mild upper respiratory infection to fulminant respiratory failure and death. HIV-infected people, especially those with co-morbidities, lower CD4 cell counts, or an unsuppressed HIV RNA viral load, may be at a higher risk of SARS-CoV-2 infection or severe disease.Immuno-suppression or regular use of antiretroviral drugs such as protease inhibitors, nucleoside reverse transfer inhibitors, or non-nucleoside reverse transfer inhibitors (NNRTI) may, on the other hand, alter the risk of SARS-CoV-2 infection and clinical presentation in this population. Immuno-compromised people are classified as a high-risk population by the Centres for Disease Control and Prevention, with people living with uncontrolled HIV or AIDS being singled out. Others, however, have suggested that using antivirals in this population may provide some protection from the virus.[2-4]

Patients who are immune-compromised have a poorer overall outcome from most serious infections, but this may vary depending on the type of immune deficiency and the pathogens. Living with the human immunodeficiency virus (HIV) is one of the most common causes of immune-compromised people worldwide, with over 1 million people living with HIV (PLWH) in the United States alone.[5]

The prevalence of HIV in India is approximately 0.22 percent, with the total number of people living with HIV/AIDS (PLHA) estimated at 21.40 lakhs, making it the world's third largest epidemic.[6]COVID19 affects approximately 37.9 million people living with HIV (PLHIV) worldwide.[7] The number of PLHIV over the age of 50 has increased dramatically as a result of antiretroviral therapy (ART) and

prevention policies, and it is estimated that more than one-fifth of PLHIV worldwide are in this age group.[8]A number of studies have been conducted to determine the effectiveness of ART on HIV-co-morbid patients. Some antiretroviral drugs have been proposed to provide protection against COVID-19,however the evidence is still inconclusive. Moreover, no any Meta-Analysis has been done till date on this area to our knowledge. Thus, this Meta-Analysis is conducted to assess the effectiveness of ART in reducing mortality in HIV/AIDS patients suffering from COVID-19.

Methodology

Search strategy

A comprehensive search was conducted from May 2021 to June 2021. Search was done using the databases: PUBMED, Medline and Scopususing the keywords "COVID-19, HIV, ART, SARS-Cov-2 and Coronavirus". No limitations were applied on study design and country of publication.

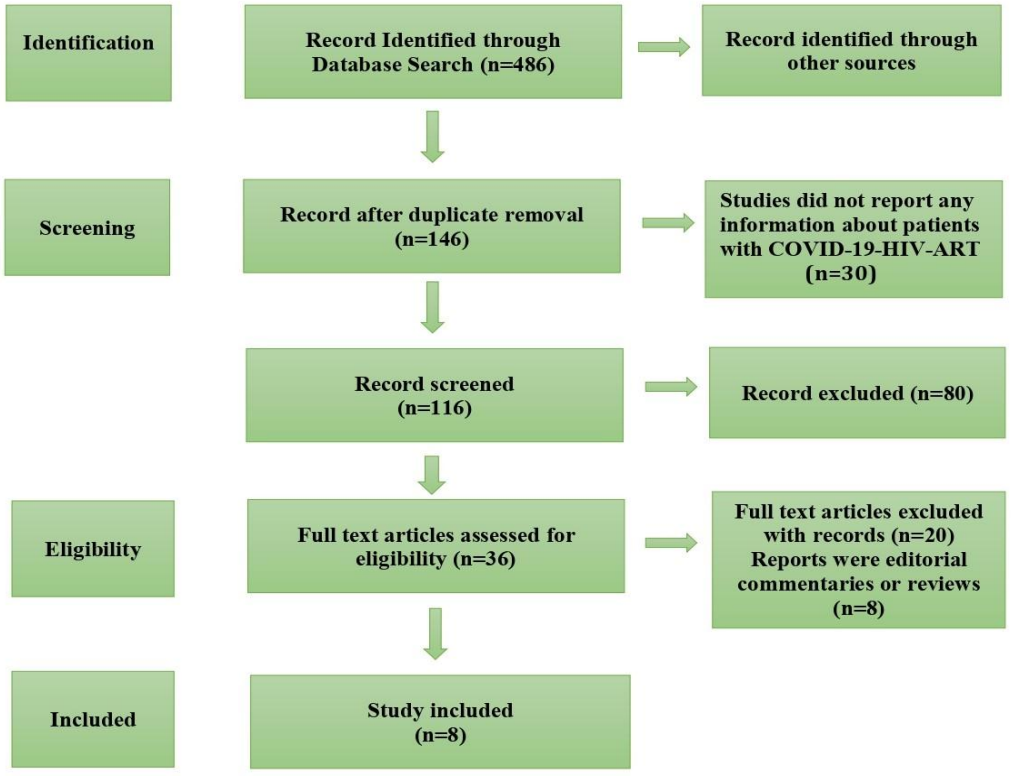

Figure 1 – Flowchart: Study Selection & Data Collection

Eligibility criteria

The inclusion criteria for the meta-analysis was as follows: (a) COVID-19 and HIV co-morbid patients receiving Anti-Retroviral Therapy (b) Articles with full text

information (c) Articles published in English language only. The exclusion criterion was (a) Small sample size (Insufficient information to pool the effectiveness).

Study Selection & Data Collection

A total of 486 studies in English language were identified from PUBMED, Medline and Scopus database using the keywords "COVID-19, HIV, ART, SARS-Cov-2 and Coronavirus.After screening abstract and full text among these publications, 146 were found to be duplicates; leaving 116 for the initial screening and 80 were then excluded based on the abstract. Among the 36 full-text articles screened, an additional 28 were excluded, leaving a total of 8 studies included for the analysis. (Figure 1)

Quality assessment

The articles shortlisted were evaluated against the inclusion and exclusion criteria. Quality assessment of articles was done using CEBM checklist for different study designs. Sixstudies were judged as good qualities (Scores of ≥8), and remaining two studies were judged as fair quality (Score 6-7). Studies rated poor (score <6) were excluded from the analysis. In the events of any disagreement between the authors, it was discussed and resolved.

Table 1
Quality & Characteristics of the included Studies

S.No.	Author and Year of Publication	Sample Size	Study design	Country	Quality Assessment Score
1	Keith Sigel et. al., 2020	4402	COHORT	USA	Good
2	Georg Harter et. al., 2020	33	CASE SERIES	Germany	Good
3	Julia del Amo et. al., 2020	77,590	COHORT	Spain	Good
4	Yousaf B. Hadi et. al., 2020	50,167	MULTI CENTRE	USA	Good
5	Anna mariaGeretti et. al., 2020	47,539	COHORT	UK	Fair
6	NogaShalev et. al., 2020	2159	CASE SERIES	USA	Fair
7	PilarVizcarra et. al., 2020	51	COHORT	Spain	Good
8	Aydin OA et. al., 2020	4	CASE SERIES	Turkey	Good

Data extraction

The following information was extracted from each of the article, cross-checked and recorded on electronic form: (a) publication details (names of the authors and

year of publication), (b) the total sample size for each study, (c) age group of the participants, (d) the proportion of male and female, (e) the study location, and (f) the effectiveness of ART in each article.

Statistical analysis

All statistical analysis was done using STATA version 16 based on random effect model. The random effect model was used because it assumes varying effect sizes between studies, because of differing study designs and study population. Between-study heterogeneity was assessed with the I^2, which describes the percentage of variability among effect estimates beyond that expected by chance. Begg's and Egger's test was performed to determine publication bias.

Results

Characteristics of the included Studies

This Meta-Analysis includes 8 studies which represent Germany, Spain, USA, UK and Turkey. Four studies were Cohort (50%), three were Case Series (37.5%), and one study was Multi-Centre (12.5%). Half of the studies were from Europe (50%), three studies were from North America and one from Asia. The articles that were ultimately included contained a total of 181,945 sample size; of them the highest sample size reported was 1,25,213 (68.81%) in Europe, 56,728 (31.17%) were reported in North America whereas the smallest sample size was 4 (0.02%) from Asia. The mean age among all the studies was 49.5 years. (Table 1)

Table 2
Characteristics of the studies included in the meta-analysis

S.No.	Author and Year of Publication	Age Group	Sample Size	Study Design	Country	Effect Size	SE
1	Keith Sigel et. al., 2020	54-67	4402	COHORT	USA	79	0.613901
2	Georg Harter et. al., 2020	26-70	33	CASE SERIES	Germany	91	4.981785
3	Julia del Amo et. al., 2020	20-79	77,590	COHORT	Spain	91.5	0.100119
4	Yousaf B. Hadi et. al., 2020	>10	50,167	Multi-centre study	USA	95.05	0.096843
5	Anna mariaGeretti et. al., 2020	≥18	47539	COHORT	UK	74.8	0.199125
6	NogaShalev et. al., 2020	23-89	2159	CASE SERIES	USA	74.1	0.942828
7	PilarVizcarra et. al., 2020	≥18	51	COHORT	Spain	96	2.743977
8	Aydin OA et. al., 2020	34-44	4	CASE SERIES	Turkey	75	21.65064

Note: SE- Standard Error

Characteristics of Included Patients

The total number of participants were 1,81,945.Among them, a Cohort Study conducted in USA had only female participants whereas a case series study conducted in Istanbul had only male participants. Remaining all the other 6 studies consisted of bothgenders. Out of total study participants, over 92.2% of PLWHA were on ART therapy. ART was associated with a higher effectiveness among HIV & SARS-CoV-2 infection (Effect Size 85.41; 95% CI; 78.35-92.48). Between-study variation was high ($I^2 = 99.94\%$, $p = 0.00$). In comparison to all the studies included, study conducted by NogaShalevet. al. had low effectiveness (74.10%).Similarly highest effectiveness was seen in study conducted by PilarVizcarraet. al. (Figure 2)

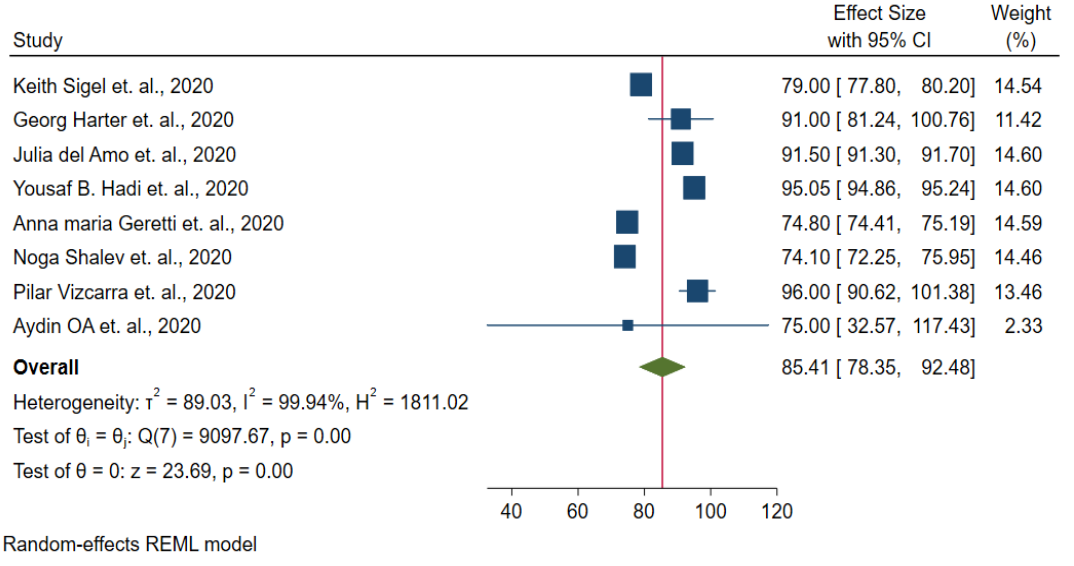

Figure 2 - Forest Plot: Characteristics of Included Patients

Publication Bias

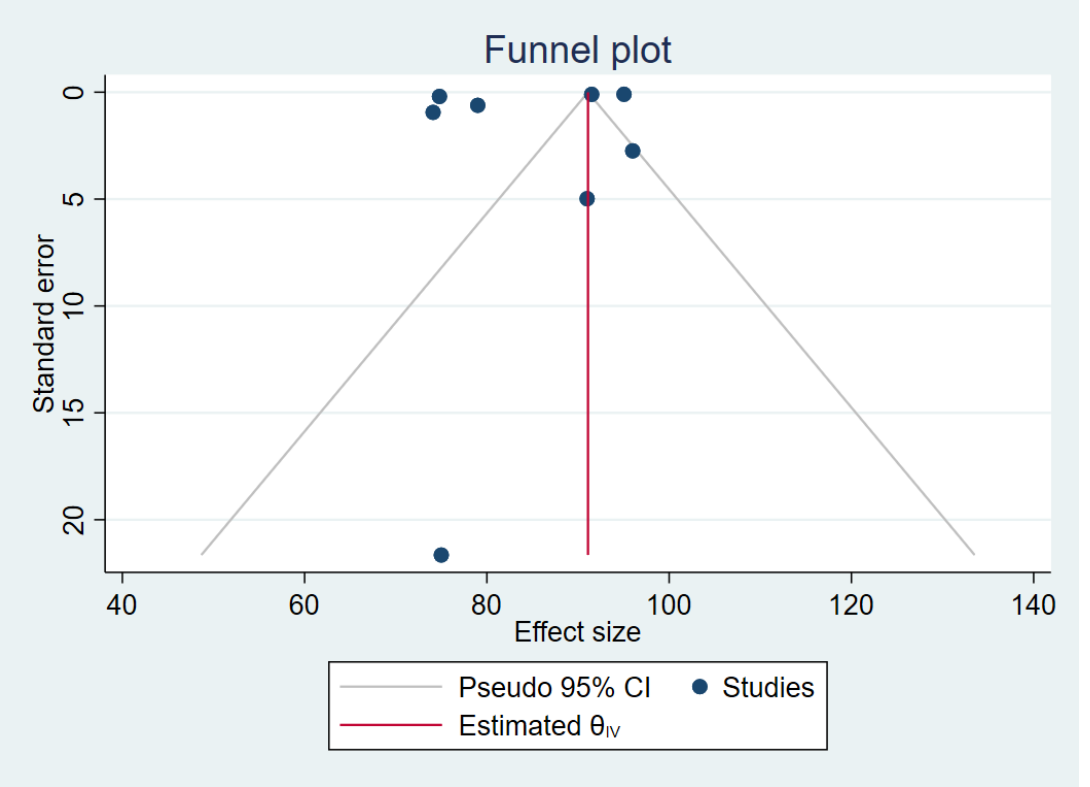

Figure 3 – Funnel Plot: Publication Bias

As shown in figure 3, publication Bias was seen through the visual inspection of funnel plot, Begg's and Egger's test and it represents asymmetrical distribution. The Begg's Ranked Correlation test for funnel plot (Kendall's $\tau = 4$) as well as Egger's Regression Test for funnel plot ($z = 0.04$) was statistically not significant ($p>0.05$).

Discussion

The present study is the first meta-analysis assessing the effectiveness of ART in reducing mortality in HIV/AIDS patients suffering from COVID-19 to our knowledge. A total of 8 studies were included in this meta-analysis, of which four were Cohort, three were Case-series and one was a Multi-centre study. Fifty percent of the studies were from Europe, three were from North America and one was from Asia.

The pooled effectiveness of ART in reducing mortality among COVID-19 and HIV Co-morbid patients is 85.4% as revealed by the present meta-analysis. All articles in this study showed the effectiveness to be ranged from 75%-96%. Thus, this result may support the hypothesis that ART is effective in reducing the mortality in COVID-19 and HIV Co-morbid patients. A high level of heterogeneity was seen

among the studies ($I^2 = 99.94\%$, $p = 0.00$). This might be due to variation in study designs as this study included 3 case series, 4 cohort and a multi-centre study. Another reason for variation among the studies might be due to the use of different ART regimens among the patients in the studies. Three types of different regimens were found to be given in the studies included. A case series conducted by NogaShalev et.al and a cohort study conducted by Keith Sigel et.al in New York, had used Integrase Strand Transfer Inhibitor (INSTI) as their ART regimens.[9,5] The effectiveness INSTI based ART regimen was less than 80%.Similarly, Aydin OA et.al. in their case series had given anti-viral therapy (Oseltamivir) to the patients and the effectiveness of this regimen was seen to be 75%.[10] In contrast to this, a case series conducted by George Harter et.al and a cohort study conducted by Julia delAmo et.al. had given Nucleoside Reverse Transcriptase Inhibitors (NRTIs) ART regimen along with NNRTI or Protease Inhibitor to their patients where the effectiveness of the drugs was more than 90%.[11,12]This might suggest a conclusion that ART regimen NRTIs along with NNRTI or Protease Inhibitor is more effective than other regimens in reducing mortality among COVID/HIV co-morbid patients.

Publication bias was seen in the present study and asymmetrical distribution was found. This can be reasoned due to the difference in study designs. Study conducted by Aydin OA Et.al. had least sample size of four whereas in a study, conducted by Julia del Amo et.al.hadmaximum sample size of 77,590.[10,11]Similarly, the study protocol among the studies also varied. Another reason for the publication bias to be seen may be due to small number of studies i.e. 8 included in this meta-analysis.

While comparing the effectiveness of the drugs based on the gender and age group of patients in the studies, we found that the effectiveness to be almost similar. This states that the drugs work equally irrespective of age and gender.[5,10]A cohort study conducted by Julia delAmo et.al. showed that the risk for COVID-19 diagnosis and hospitalization were greater in people aged 70 years and above.In contrast to this, Anna Mariaet.al. explained in their study that the risk for mortality was higher in the age group below 60 years. This can be explained asthe effectiveness of ART and risk for mortality might not depend on age and gender.[11,13]

A comparison of effectiveness of drugs was done among studies with different sample size. A study conducted by PilarVizcarra et.al with a sample size of 51 showed the effectiveness of 96%. Similarly, almost same level of effectiveness (95.05%) was seen in the study conducted by Yousaf B, Hadi et.al. with a higher sample size of 50,167. In conclusion, effectiveness of drugs is same irrespective of the sample size in the study.[14,15]

Conclusion

The finding of this study have to be read with caution as there were no studies from developing countries that met the inclusion criteria. The findings of this study conclude that HIV patients receiving Anti-Retroviral Therapy and infected by COVID-19 disease have less risk of severity and mortality comparatively. The effectiveness of ART on HIV – COVID co-morbid patients was found to be

85.41.Further studies are warranted to assess the outcome of ART in reducing mortality among HIV/AIDS patients suffering from COVID-19.

Limitations

Among the 8 selected studies, three studies hadsmall sample size. Most of the studies were case series and cohort studies that did not adequately account for confounding variables. Furthermore, all the included studies were conducted in developed countries which may limit the applicability to populations of developing and under developed countries.

Conflict of Interest
The authors declare no conflict of interest

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