Hydroxychloroquine Pre-Exposure Prophylaxis for COVID-19 in Healthcare Workers in India: Meta-Analysis

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Abstract

Background: While vaccines have taken center stage in the battle against COVID-19, alternate approaches for prevention of SARS-CoV-2 infection have been ignored.

Methods: We analyzed ten nonrandomized controlled trials of hydroxychloroquine (HCQ) pre-exposure prophylaxis (PrEP) involving 4,909 healthcare workers (HCWs) in India. We used random-effects meta-analysis to summarize infection risk ratios across the studies.

Results: Weekly HCQ PrEP taken for any length of time significantly reduced SARS-CoV-2 infection (risk ratio 0.56, 95% CI 0.37-0.83, P=.0040), while weekly HCQ PrEP taken for six weeks or more in a subset of 2,255 HCWs produced an even greater reduction in SARS-CoV-2 infection (risk ratio 0.21, 95% CI 0.06-0.67, P=.0088). The weekly HCQ PrEP regimen was well tolerated in all studies.

Conclusions: Weekly HCQ PrEP appeared to be effective for prevention of COVID-19 in high-risk HCWs from India. Further studies are warranted of HCQ PrEP to supplement vaccines in the prevention of COVID-19.

Introduction

To date, the COVID-19 pandemic has resulted in more than 169 million registered cases of SARS-CoV-2 infection and more than 3.5 million deaths world-wide.[1] Although novel COVID-19 vaccines have become clinically available, the efficacy and long-term safety of these vaccines remain uncertain, particularly in population subgroups, and their availability in resource-poor countries may be limited.[2,3] Alternate approaches for prevention of disease have received little attention, and one medication, hydroxychloroquine (HCQ), has been attacked and dismissed based on flawed studies and political controversy that obscured the potential value of this treatment as pre-exposure prophylaxis (PrEP) for SARS-CoV-2 infection.[4]

A British study of 120,075 healthcare workers (HCWs) found that these subjects had a 7-8-fold greater risk of developing severe COVID-19 compared to non-HCWs.[5] With this background, prior to the availability of COVID-19 vaccines, a number of HCQ PrEP cohort study trials were conducted in HCWs from India in 2020. We performed a meta-analysis of these studies to evaluate the efficacy of weekly HCQ PrEP for prevention of COVID-19.

Materials and Methods

We performed a search of the medical literature using PubMed, Google Scholar, medRxiv and ResearchGate to obtain all relevant publications and preprints. Inclusion and exclusion criteria are listed in Table 1. The initial search yielded 1,290 results. Following removal of misclassified and duplicate citations, we were left with 14 publications on HCQ PrEP. Ten of these publications described weekly HCQ PrEP in HCWs from India, and these studies were included in the meta-analysis, as shown in Figure 1.

We analyzed data using the random effects meta-analysis model (DerSimonian and Laird method).[6] Results used the inverse variance method for weighting. Analyses by the fixed-effects model were virtually identical. We assessed heterogeneity between studies by visual inspection of funnel forest plots, by estimation of I^2 statistics ($I^2 \geq 60\%$ was considered substantial heterogeneity) and their statistical significance for the heterogeneity and, where possible, by subgroup analysis.[7] Where evidence of substantial heterogeneity was found, the possible reasons for this were investigated.

Results

Ten cohort studies of weekly HCQ PrEP were evaluated, as shown in Table 2.[8-17] These studies enrolled a total of 4,909 high-risk HCWs. Sixty-two percent were men and 38% were women, and the mean age as described in eight of the ten studies was 33.1 ± 7.7 years. Among subjects at risk, 63% were involved in direct patient care (doctors and nurses) while 37% were hospital support staff (laboratory technicians, housekeeping staff, security guards and others). All ten studies examined the prophylactic effect of weekly HCQ PrEP taken for any lengths of time, while a subset of four of the ten studies involving 2,453 HCWs also examined the prophylactic effect of weekly HCQ PrEP taken for six weeks or more, and five of the ten studies, involving 2,787 HCWs, examined prophylactic use for less than six weeks.

In nine of the ten studies, a HCQ loading dose was used (400mg BID on day one), as recommended by the Indian Council of Medical Research (ICMR) National Taskforce for COVID-19.[18] In the tenth study a loading dose was not specified. All ten studies used HCQ PrEP dosing of 400mg weekly after the initial dose, as recommended by the ICMR guidelines. Testing for SARS-CoV-2 infection was performed using reverse-transcriptase PCR in eight studies (References 8, 9, 13-17, and Khurana A, personal communication, April 14, 2021) and serological methods in two studies (References 11 and 12).

Six of the ten studies demonstrated significantly decreased risk ratios (RRs) of SARS-CoV-2 infection in subjects who had used weekly HCQ PrEP for any lengths of time compared to those who did not use HCQ, as shown in Table 3. The overall RR using random effects (RE) meta-analysis was 0.56 (95% CI 0.37-0.83, P=.0040), Figure 2. HCWs who took HCQ PrEP for less than six weeks (five studies) did not show a significant decrease in risk of viral infection (RR 1.15, 95% CI 0.76-1.74, P=.52), Figure 3. In HCWs who took weekly HCQ PrEP for six weeks or more (four studies), the infection proportion was substantially reduced. The overall RR using RE meta-analysis was 0.21 (95% CI 0.06-0.67, P=.0088), Figure 4. The heterogeneity I^2 values were less than 30% and not statistically significant in all three meta-analyses.

A measure of dose-response in duration of HCQ PrEP usage can be obtained by comparing results of the longer-usage categories to results of the shorter-usage categories. Four studies included results for both less than 6 weeks of use and for 6 or more weeks of use. [8,10-12] Risk of infection was significantly lower (P=.0039) for longer use. One other study provided results for

HCQ PrEP use less than 6 weeks. [13] Including that study among the other four with short-term use still resulted in significantly lower risk with longer HCQ PrEP use (P=.0092).

Adverse events (AEs) related to HCQ PrEP were reported in three of the ten studies, as shown in Table 4. The most common AEs were headache (8%) followed by nausea (6%) and dyspepsia (6%). No arrhythmias were reported by the HCWs. AEs were generally mild and well tolerated, as shown in one study where the HCQ discontinuation rate due to AEs was 4%.[13] The rate of AEs was consistent with other safety studies of HCQ use in COVID-19 trials and therapy of pregnant women and children.[19-23]

Discussion

Our meta-analysis suggests that weekly HCQ PrEP is effective in preventing COVID-19 in a high-risk group of HCWs after PrEP has been given for an adequate length of time in the face of exposure to SARS-CoV-2. It is important to recognize that these studies exclusively analyzed HCQ PrEP and excluded HCQ post-exposure prophylaxis (PEP) or treatment of SARS-CoV-2-infected individuals. Lumping of these groups in prior studies has resulted in flawed analysis and inaccurate conclusions about the safety and efficacy of HCQ PrEP.

For example, a recent review of HCQ therapy to "prevent COVID-19" by the World Health Organization listed six randomized controlled trials (RCTs): three were clearly described as PEP studies, while the remaining three stated that the trials were underpowered to draw conclusions about HCQ PrEP.[24] The inconsistent results of HCQ PEP versus the apparent benefit of HCQ PrEP for COVID-19 is reminiscent of the divergent effects of PEP and PrEP regimens for reliable prevention of HIV infection during the AIDS pandemic.[25-27] While the PEP studies were described as examinations of infection prevention, subjects were enrolled days after exposure and therefore should properly have been classified as receiving early treatment, since full prevention with HCQ PrEP requires the cumulative equivalent of six or more weekly doses, as shown in the India studies reviewed here.

While our literature review identified 14 studies of HCQ PrEP, we only analyzed the ten studies from India because they were performed in HCWs using weekly HCQ regimens with dosing based on the ICMR guidelines and similar to the standard of care for malaria prophylaxis.[1,18] The other four trials were performed in other countries (two in USA, two in Spain) using higher dose

PrEP protocols (daily or twice-weekly regimens) that produced adverse events that were not observed in the weekly HCQ PrEP studies from India. Despite these drawbacks, the two studies with adequate numbers of outcomes also showed reduced risks similar to the India studies.[28-31] Excessive dosing has led to the public perception that HCQ is a dangerous drug.[32,33] In contrast, the HCQ PrEP studies from India used dosing of 2,400mg over 5-6 weeks according to the ICMR protocol, and this approach avoids potential treatment complications as reported with aggressive HCQ regimens used in trials from other countries.

A strength of this meta-analysis is its demonstration of dose-response benefit in risk reduction with increased duration of HCQ PrEP, and the fact that approximately 2,400mg of HCQ taken over 5-6 weeks is necessary to achieve full risk-reduction benefit. Despite the advantage of a uniform treatment approach across the India studies, our meta-analysis has several limitations. Cohort trials with subjective outcomes may introduce recall bias, but the use of objective viral testing as the endpoint should alleviate this bias in the India studies.[34,35] The younger age of subjects distinguishes them from other groups at high risk for COVID-19, but the high risk for COVID-19 in HCWs puts them on a par with susceptibility of older patients at risk for SARS-CoV-2 infection.

None of the studies analyzed here were randomized trials, but well-conducted nonrandomized trials have been extensively shown to provide results equivalent to high-quality RCTs in a "real world" setting.[1,36] The India studies examining HCQ PrEP over time had protocols for six or more weeks of use; thus participants who contributed data for shorter treatment durations likely stopped their protocols because of viral infection, biasing the medication result away from benefit for the evaluation of shorter-term use. This problem is unavoidable in carrying out studies where subjects cannot receive adequate initial doses prior to virus exposure. Although the studies showed prevention of viral infection, they were not designed to show severity of infection in subjects who tested positive for SARS-CoV-2, and it is unclear if HCQ PrEP attenuated disease symptoms in treated subjects. None of the ten India studies had any deaths in either the HCQ or control subjects.

The effect of other prophylactic modalities such as personal protective equipment, handwashing, nutritional supplements or prior or recent BCG vaccination may conceivably have influenced the study results, but these modalities would tend to be evenly distributed between treated subjects

and controls. Other PrEP medications such as ivermectin may also be effective in the HCW setting, and a head-to-head comparison with these medications is lacking in the medical literature.[17,37] Despite these limitations, our meta-analysis suggests that HCQ PrEP could serve as a stop-gap or fill-in approach to COVID-19 prevention until universal immunity of the population at risk is achieved.

Conclusions

Weekly HCQ PrEP appeared to be effective for prevention of COVID-19 in high-risk HCWs from India. Further studies of HCQ PrEP are warranted to supplement vaccines in the prevention of COVID-19.

Competing Interest Statement

The authors deny any financial relationships during the previous three years with any organizations that might have interests in the submitted work, or any other relationships or activities that could appear to have influenced the submitted work.

Patient and Public Involvement

Patients were not directly involved in the research. However, the results of our study could affect hundreds of millions of people around the world.

Figure Legends

Figure 1: Flow Diagram of Study Screening and Selection.

Figure 2: Forest Plot of HCQ PrEP Studies: HCQ PrEP Any Duration. Funnel plot (i.e., in order of decreasing standard error or confidence interval width) of the risk ratios of the 10 HCQ PrEP studies. In this and subsequent funnel plots, the area of each square is proportional to the study weight in the analysis; the horizontal bars indicate each study's 95% confidence interval; and the diamonds below represent the summary result, with width equal to the summary 95% confidence interval.

Figure 3: Forest Plot of HCQ PrEP Studies: HCQ PrEP < 6 Weeks

Figure 4: Forest Plot of HCQ PrEP Studies: HCQ PrEP ≥ 6 Weeks

References

1. Stricker RB, Fesler MC. Flattening the risk: Pre-exposure prophylaxis for COVID-19. *Infect Drug Resist*. 2020 Oct 19;13:3689-3694. https://doi.org.10.2147/IDR.S264831.

2. Haynes BF, Corey L, Fernandes P, et al. Prospects for a safe COVID-19 vaccine. *Sci Transl Med*. 2020 Nov 4;12(568):eabe0948. https://doi.org.10.1126/scitranslmed.abe0948.

3. Suzuki YJ, Gychka SG. SARS-CoV-2 spike protein elicits cell signaling in human host cells: Implications for possible consequences of COVID-19 vaccines. *Vaccines (Basel)*. 2021 Jan 11;9(1):36. https://doi.org.10.3390/vaccines9010036.

4. Berry AC, Gonnering RS, Rodriguez I, Zhang Q, Berry BB. Unfavorable hydroxychloroquine COVID-19 research associated with authors having a history of political party donations. *Rev Cardiovasc Med*. 2021;22:191-198. https://doi.org/10.31083/j.rcm.2021.01.262.

5. Mutambudzi M, Niedwiedz C, Macdonald EB, et al. Occupation and risk of severe COVID-19: prospective cohort study of 120 075 UK Biobank participants. *Occup Environ Med*. 2020, Nov 4. https://doi.org.10.1136/oemed-2020-106731.

6. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986; 7: 177-88.

7. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Stat Med* 2010; 29: 3046–67.

8. Chatterjee P, Anand T, Singh KJ, et al. Healthcare workers and SARS-CoV-2 infection in India: a case-control investigation in the time of COVID-19. *Indian J Med Res*. 2020;151(5):459–467. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7530442/.

9. Bhattacharya R, Chowdhury S, Mukherjee R, et al. Pre exposure hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers. *MedRxiv*. 2020. https://doi.org/10.1101/2020.06.09.20116806.

10. Khurana A, Kaushal GP, Gupta R, Verma V, Sharma K, Kohli M. Prevalence and clinical correlates of COVID-19 outbreak among health care workers in a tertiary level hospital in Delhi. *Am J Infect Dis*. 2021 (in press). https://doi.org/10.1101/2020.07.21.20159301.

11. Goenka MK, Afzalpurkar S, Goenka U, et al. Seroprevalence of COVID-19 amongst health care workers in a tertiary care hospital of a metropolitan city from India. *J Assoc Physicians India.* 2020 Nov;68(11):14-19. https://pubmed.ncbi.nlm.nih.gov/33187030/.

12. Yadav RM, Pate A, Shankarkumar A, et al. Sero-survey for health-care workers provides corroborative evidence for the effectiveness of Hydroxychloroquine prophylaxis against COVID-19 infection. *J Epidemiol Global Health* 2021 (in press). Available at: https://www.researchgate.net/publication/344221734.

13. Kadnur HB, Aggarwal A, Soneja M, et al. Hydroxychloroquine pre-exposure prophylaxis for COVID-19 among healthcare workers: Initial experience from India. *Lancet Preprints* 2020. Available at: http://dx.doi.org/10.2139/ssrn.3622350.

14. Dev N, Meena RC, Gupta DK, Gupta N, Sankar J. Risk factors and frequency of COVID-19 among healthcare workers at a tertiary care centre in India: a case–control study, Trans Royal Soc Trop Med Hyg, 2021; trab047. https://doi.org/10.1093/trstmh/trab047

15. Mathai SS, Behera V, Hande V. Hydroxychloroquine as pre-exposure prophylaxis against COVID-19 in health-care workers: A single-center experience. J Mar Med Soc 2020;22:S98-104. https://doi.org/10.4103/jmms.jmms_115_20

16. Datta D, Ghosal S, Sinha B, et al. No role of HCQ in COVID-19 prophylaxis: A survey amongst Indian doctors. J Vaccines Vaccin. 2020;S6:002.

17. Behera P, Patro BK, Singh AK, Chandanshive PD, S. R. R, Pradhan SK, et al. Role of ivermectin in the prevention of SARS-CoV-2 infection among healthcare workers in India: A matched case-control study. PLoS ONE 2021;16(2): e0247163. https://doi.org/10.1371/journal.pone.0247163

18. Indian Council of Medical Research National Taskforce for COVID-19. Advisory on the use of Hydroxychloroquine as prophylaxis for SARS CoV2 infection. March 22, 2020. Available at: https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf.

19. Lofgren SM, Nicol MR, Bangdiwala AS, et al. Safety of hydroxychloroquine among outpatient clinical trial participants for COVID-19. *Open Forum Infect Dis*. 2020;7:ofaa500. https://doi.org/10.1093/ofid/ofaa500.

20. Sogut O, Can MM, Guven R, et al. Safety and efficacy of hydroxychloroquine in 152 outpatients with confirmed COVID-19: A pilot observational study. *Am J Emerg Med*. 2020 Dec 11;40:41-46. https://doi.org.10.1016/j.ajem.2020.12.014.

21. Fesler MC, Stricker RB. Pre-exposure prophylaxis for COVID-19 in pregnant women. *Int J Gen Med*. 2021;14:279-284. https://doi.org/10.2147/IJGM.S295627.

22. Mukhopadhyay S, Paul S, Samanta B. Hydroxychloroquine in the prophylaxis of COVID 19: A survey of safety on the healthcare workers in India. *Perspect Clin Res*. 2021 Jan-Mar;12(1):58-59. doi: 10.4103/picr.PICR_310_20.

23. Risch HA. Early outpatient treatment of symptomatic, high-risk COVID-19 patients that should be ramped up immediately as key to the pandemic crisis. *Am J Epidemiol*. 2020 Nov 2;189(11):1218-1226. doi: 10.1093/aje/kwaa093.

24. Lamontagne F, Agoritsas T, Siemieniuk R, et al. A living WHO guideline on drugs to prevent covid-19. *BMJ* 2021;372:n526. https://doi.org/10.1136/bmj.n526.

25. Cohen MS, Kashuba AD, Gay C. HIV antiretroviral postexposure prophylaxis: a cautionary note. *Clin Infect Dis*. 2005;41(10):1514–1516.

26. Kijak GH, Kim JH. Timing, adherence, resistance, and ... persistence? New insight into the mechanisms of failure of HIV type 1 postexposure prophylaxis. *J Infect Dis*. 2013;208(10):1542-1544. https://doi.org/10.1093/infdis/jit486.

27. Koss CA, Havlir DV, Ayieko J, et al. HIV incidence after pre-exposure prophylaxis initiation among women and men at elevated HIV risk: A population-based study in rural Kenya and Uganda. *PLoS Med*. 2021 Feb 9;18(2):e1003492. https://doi.org/10.1371/journal.pmed.1003492.

28. Rajasingham R, Bangdiwala AS, Nicol MR, etal. Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. *Clin Infect Dis* 2020;ciaa1571. doi: 10.1093/cid/ciaa1571.

29. Abella BS, Jolkovsky EL, Biney BT, etal. Prevention and Treatment of COVID-19 With Hydroxychloroquine (PATCH) Investigators. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. *JAMA Intern Med* 2021;181:195-202. doi: 10.1001/jamainternmed.2020.6319

30. Revollo B, Tebe C, Peñafiel J, et al. Hydroxychloroquine pre-exposure prophylaxis for COVID-19 in healthcare workers. *J Antimicrob Chemother*. 2021 Feb 11;76(3):827-829. doi: 10.1093/jac/dkaa477.

31. Grau-Pujol B, Camprubí D, Marti-Soler H, et al. Pre-exposure prophylaxis with hydroxychloroquine for COVID-19: initial results of a double-blind, placebo-controlled randomized clinical trial. *Research Square* 2021; doi: 10.21203/rs.3.rs-72132/v1.

32. RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19: preliminary results from a multicentre, randomized, controlled trial. *MedRxiv*. 2020 https://doi.org/10.1101/2020.07.15.20151852.

33. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 - Interim WHO Solidarity trial results. *N Engl J Med*. 2021 Feb 11;384(6):497-511. doi: 10.1056/NEJMoa2023184.

34. Coughlin SS. Recall bias in epidemiologic studies. *J Clin Epidemiol*. 1990;43(1):87-91. doi: 10.1016/0895-4356(90)90060-3.

35. Drews CD, Greenland S. The impact of differential recall on the results of case-control studies. *Int J Epidemiol* 1990;19:107–12.

36. Anglemyer A, Horvath HT, Bero. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: MR000034. DOI: 10.1002/14651858.MR000034.pub2.

37. Morgenstern J, Redondo JN, Olavarria A, et al. Retrospective cohort study of ivermectin as a SARS-CoV-2 pre-exposure prophylaxis method in healthcare workers. *MedRxiv.* 2021. doi: https://doi.org/10.1101/2021.04.10.21255248.

Table 1: Study Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
Adults >18yo	Children <18yo
Healthcare workers including support staff	Non-healthcare workers
Hydroxychloroquine in study	No hydroxychloroquine in study
India	Non-Indian Countries
Before COVID-19 vaccines, 2020	After COVID-19 vaccine rollout, 2021
Pre-exposure prophylaxis	Post-exposure prophylaxis
Study not limited to rheumatological disease subjects	Rheumatological disease subjects

Table 2: Demographics of Healthcare Worker Studies[8-17]

Subjects at risk	**Value (%)**
Sex*	
Male	2687 (62)
Female	1670 (38)
Age*	
Mean Age ± SD (years)	33.1 ± 7.7
Occupation*	
Direct patient care (Doctors, nurses)	2939 (63)
Support staff (Lab, housekeeping, etc.)	1699 (37)

*Available for 8/10 studies

Table 3: HCQ PrEP Studies in Healthcare Workers in India

Study	HCQ* (n)	No HCQ (n)	RR (95% CI)	P-value
1. Chatterjee et al., 2020	365	386		
Infection	172	193	0.90 (0.60-1.35)	.62
HCQ≥6 doses	12	56	0.04 (0.01-0.16)	$10^{-5.3}$
2. Bhattacharya et al., 2020	54	52		
Infection	4	20	0.19 (0.07-0.53)	.0013
HCQ≥6 doses	NA			
3. Khurana et al., 2020	90	91		
Infection	54	40	1.36 (1.02-1.82)	.033
HCQ≥6 doses	6	16	0.62 (0.30-1.28)	.19
4. Goenka et al., 2020	237	885		
Infection	19	115	0.62 (0.39-0.98)	.041
HCQ≥6 doses	1	76	0.10 (0.01-0.71)	.021
5. Yadav et al., 2020	178	221		
Infection	17	27	0.78 (0.44-1.39)	.40
HCQ≥6 doses	6	119	0.39 (0.17-0.93)	.033
6. Kadnur et al., 2020	248	86		
Infection	2	5	0.14 (0.03-0.70	.017
HCQ≥6 doses	NA			
7. Dev et al., 2020	260	499		
Infection	155	351	0.74 (0.61-0.90)	.0024
HCQ≥6 doses	NA			
8. Mathai et al., 2020	491	113		
Infection	10	22	0.10 (0.05-0.21)	$10^{-9.1}$
HCQ≥6 doses	NA			
9. Datta et al., 2020	146	135		
Infection	16	19	0.78 (0.42-1.45)	.43
HCQ≥6 doses	NA			
10. Behera et al., 2020	186	186		
Infection	7	12	0.56 (0.19-1.63)	.29
HCQ≥6 doses	NA			
Total				
Number at Risk	2,255	2,654		
Infection	456 (20%)	817 (31%)	0.56 (0.37-0.83)	.0040
HCQ≥6 doses	292			
Infection	25 (8.6%)		0.21 (0.06-0.67)	.0088

HCQ, hydroxychloroquine; PrEP, pre-exposure prophylaxis; NA, not available; RR, risk ratio; CI, confidence interval

*Any duration of HCQ PrEP use unless stated otherwise.

Table 4: Adverse Events Reported by HCWs Taking HCQ PrEP

	Chatterjee et al.[8]	**Bhattacharya et al.[9]**	**Kadnur et al.[13]**	**Total (%)**
Number on HCQ	365	54	248	667
Nausea	23	0	21	44 (7%)
Headache	20	2	30	52 (8%)
Vertigo	0	0	21	21 (3%)
Irritability	0	0	9	9 (1%)
Diarrhea	17	0	9	26 (4%)
Palpitations	1	0	5	6 (1%)
Dyspepsia	14	16	10	40 (6%)
Rash/Allergy	4	3	8	15 (2%)
Arrhythmia	0	0	0	0 (0%)

Figure 1: Flow Diagram of Study Screening and Selection

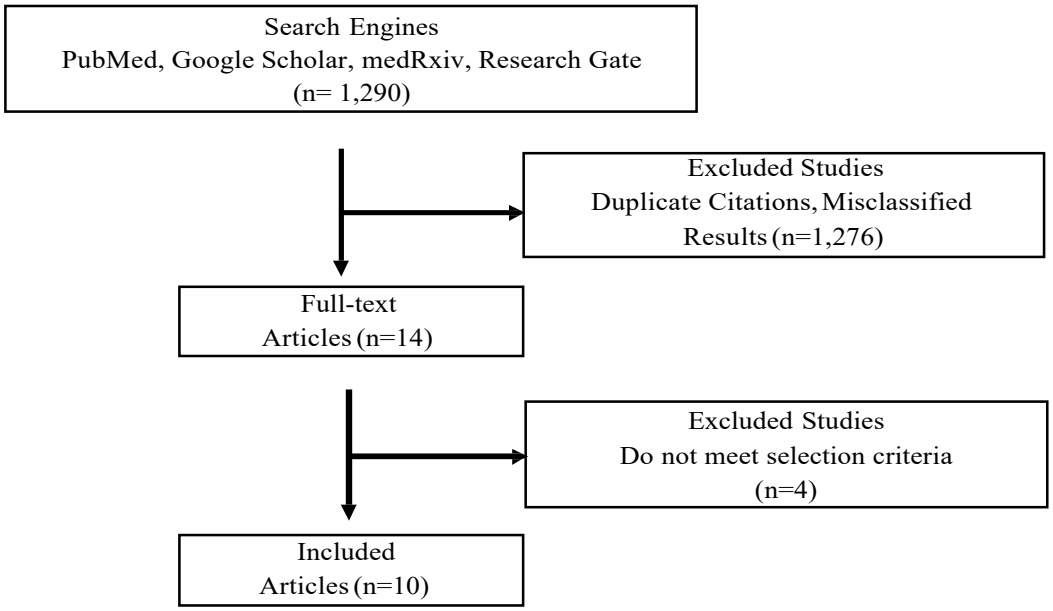


Figure 2: Forest Plot of HCQ PrEP Studies: HCQ PrEP Any Duration

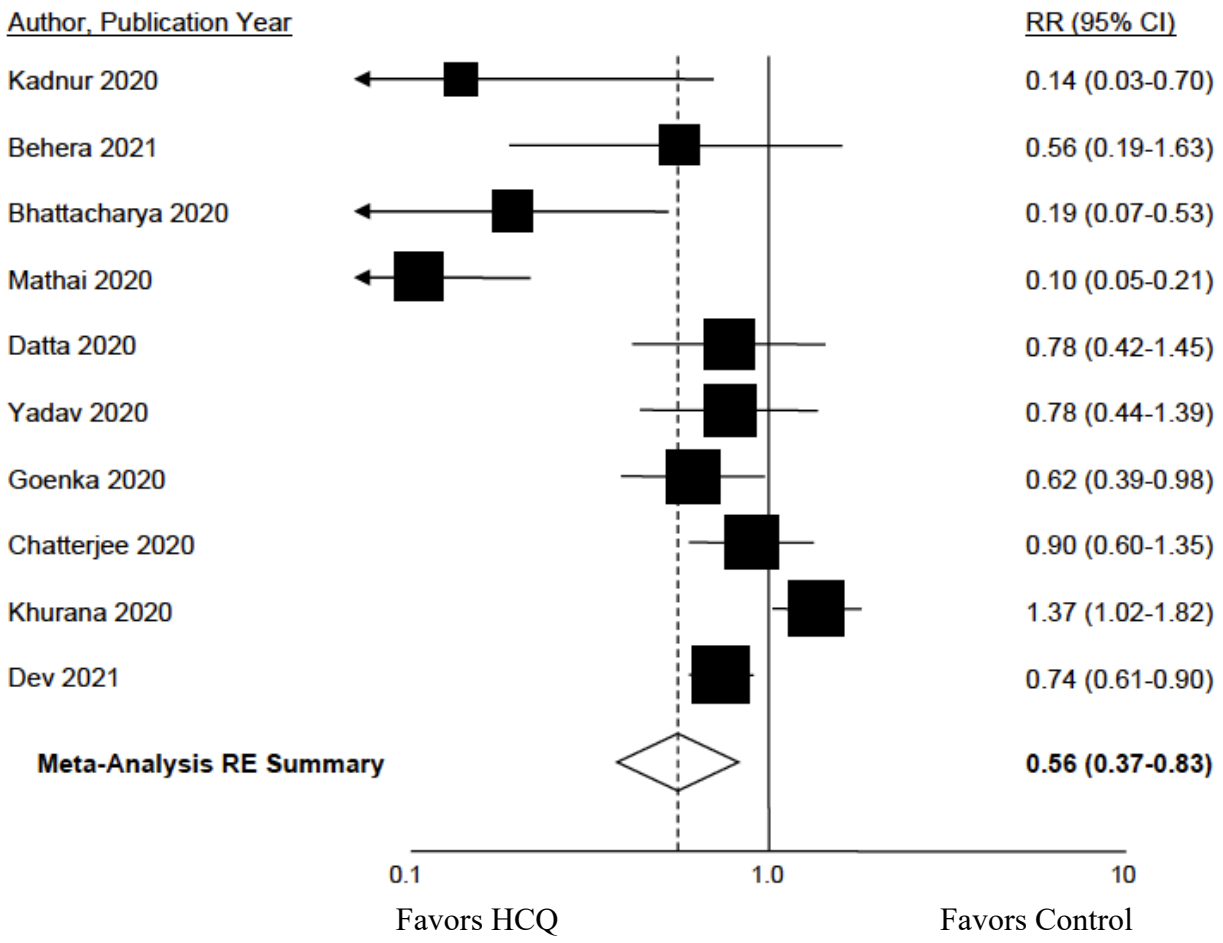


Figure 3: Forest Plot of HCQ PrEP Studies: HCQ PrEP < 6 Weeks

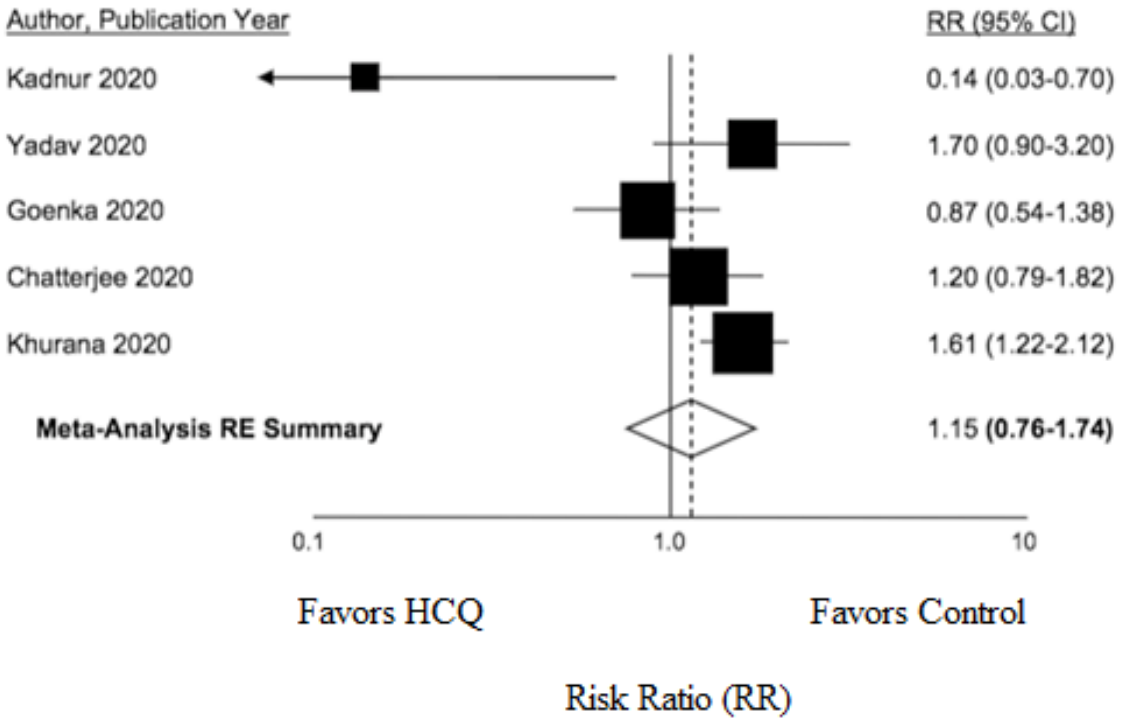
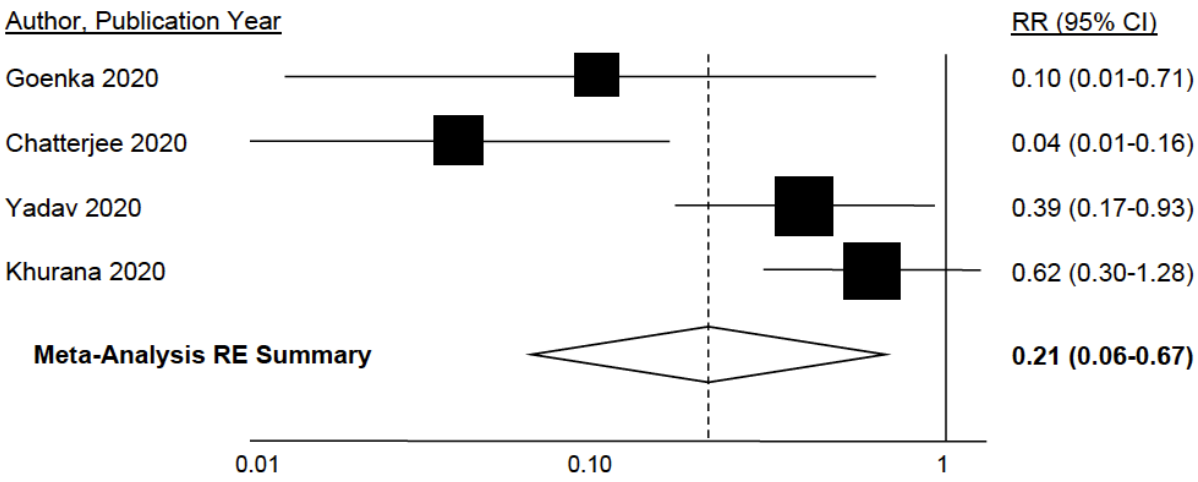


Figure 4: Forest Plot of HCQ PrEP Studies: HCQ PrEP ≥ 6 Weeks



RR (Risk Ratio)