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Is Primary *Mycobacterium avium* Complex Prophylaxis Necessary in Patients with CD4 < 50 Cells/ μ L Who Are Virologically Suppressed on cART?

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Abstract

We analyzed 369 patients with no prior *Mycobacterium avium* complex (MAC) infection and CD4 < 50 cells/ μ L (baseline), while on combination antiretroviral therapy (cART), for incidence rates of primary MAC infection during the 6 months after baseline, by prophylaxis status. Of participants (median age, 40 years old), most were male (81%) and about half were non-white; at baseline, 81% of participants were on cART > 60 days and 19% had HIV RNA < 1000 copies/mL, whereas 65% had HIV RNA > 10,000 copies/mL. Eleven patients had MAC infection within 6 months baseline (rate = 0.6/100 person months): 4/175 on MAC prophylaxis vs. 7/194, no MAC prophylaxis ($p = 0.64$). Of the 11 patients, seven had HIV RNA > 10,000, and three > 1000–9999 copies/mL at baseline (one missing). Median time to MAC infection was 62 days (IQR 43–126, maximum 139 days). No MAC infection occurred among 71 (19%) patients virologically suppressed (HIV RNA < 1000 copies/mL) at baseline, including 41 patients with no MAC prophylaxis during follow-up. A small number of eligible virologically suppressed participants and the lack of data on cART/MAC prophylaxis adherence limited our observational nonrandomized study. Primary MAC prophylaxis may not be required for cART-virologically suppressed patients with CD4 < 50 cells/mL.

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Introduction

Combination antiretroviral therapy (cART) for HIV infection improves immune function,¹ reduces morbidity and mortality,² and has resulted in the remarkable decrease in the incidence of HIV-associated opportunistic infections.^{3,4} Prior to cART availability, *Mycobacterium avium-intracellulare* complex (MAC) infection was one of the most common opportunistic infections in advanced HIV infection.⁵ The U.S.⁶ and European⁷ guidelines recommend that HIV-infected persons with absolute CD4 cell counts of < 50 cells/ μ L and no prior MAC infection be prophylaxed against this infection until their CD4 cell counts remain > 100 cells/ μ L for 3 months.

Since the incidence of MAC infections has precipitously declined in HIV-infected patients with the advent of cART,⁴ the question arises whether the current MAC chemoprophylaxis guidelines are still applicable to current clinical practice. Chemoprophylaxis against opportunistic infections caused by *Pneumocystis jiroveci*, *Cryptococcus* sp., and *Penicillium marneffei* had been safely discontinued in cART-virologically suppressed patients with CD4 cell counts of < 200 cells/ μ L.^{8,9} In this context, we examined the incidence of MAC among patients with CD4 cell counts of < 50 cells/ μ L on cART to determine whether MAC prophylaxis is necessary in this group of patients.

Methods

We conducted a retrospective analysis using data from patients enrolled in the HIV Outpatient Study (HOPS) between 1996 and 2007 who were prescribed cART and were eligible for MAC prophylaxis. The HOPS is an ongoing, open prospective observational cohort study that has continuously recruited and followed HIV-infected patients since 1993.^{2,10} Since the HOPS' inception, the study sites have included 10 clinics (six university-based, two public, two private) in eight US cities and provided care for about 3000 HIV-infected patients per year.¹⁰ The study protocol was approved and has been renewed annually by each participating institution's ethical review board. All study participants provide written, informed consent.

Eligibility for this study of MAC prophylaxis was defined as having a CD4 cell count of < 50 cells/ μ L^{6,7} and no prior MAC (clinical and microbiological) diagnosis. We calculated incidence rates of MAC per 100 person-months (pmos) of observation for the 6 months after the eligible CD4 cell count. We excluded patients when MAC infection was diagnosed within 30 days of enrollment at a HOPS site and considered these infections as prevalent. Observation ended at the diagnosis of MAC, 6 months after eligible CD4 count, at death, or patient loss to follow-up. MAC prophylaxis was defined as the prescription of azithromycin, clarithromycin, or rifabutin^{6,7} at recommended doses for at least 30 days during the 6-month period after the date of the eligible CD4 cell count determination.

MAC incidence rates were stratified by prophylaxis status and by the HIV viral load closest to the eligible CD4 cell count determination (from 180 days prior through 30 days after the eligible CD4 cell count date). All analyses were done using SAS version 9.1 (Cary, NC)

with the exception of calculating 95% confidence intervals for all rates for which we used the Open Source Epidemiologic Statistics for Public Health.¹¹

Results

There were 1257 HOPS enrollees who had at least one CD4 count of < 50 cells/ μ L from 1996 through 2007; of these patients, 369 patients were prescribed cART at the time their eligible CD4 cell count was measured. These 369 patients who met the eligibility criteria for our analysis had a median age of 40 years [interquartile range (IQR): 35–47]; were primarily male (81%) and of non-Hispanic white (48%) or black race/ethnicity (39%). The most frequent HIV transmission risk was being a man who had sex with men (58%). The study population was almost equally divided between privately insured (45%) and publicly insured (48%) patients. Eligible patients had been diagnosed with HIV infection for a median of 7.2 years (IQR: 3.3–11.0). The median eligible CD4 cell count at the time of initiation of observation was 30 cells/ μ L (interquartile range, IQR: 16–41).

Overall, 175 (47%) of 369 patients had been prescribed MAC prophylaxis for at least 30 days during the 6 months after eligible CD4 cell count; 28 (16%) of those were prescribed MAC prophylaxis for $< 50\%$ of the observation time, 33 (19%) patients for 50–99% of time, and 114 (65%) were prescribed MAC prophylaxis for the entire 6-month period. There were zero incident MAC infections among 114 persons prescribed prophylaxis 100% of observation time, and 11 MAC infections among 255 persons who were prescribed prophylaxis, none to $< 100\%$ of observation time ($p = 0.02$). Of the 11 patients with incident MAC infections, 7 were not prescribed prophylaxis, and 4 received it $< 100\%$ of observation time.

The HIV viral load closest to the eligible CD4 cell count was < 1000 copies/mL for 71 (19%) patients, 1000–10,000 for 31 (8%) patients, and $> 10,000$ copies/mL for 240 (65%) patients; 27 (7%) had missing viral loads (Table 1). The frequency of prophylaxis prescription was 42% (30/71) among patients with the viral load < 1000 copies/mL, and it was 52% (16/31) and 50% (120/240) among those with viral loads 1000–10,000 and $> 10,000$ copies/mL, respectively. There were no statistically significant demographic differences in the frequency of MAC prophylaxis prescription (data not shown).

Eleven MAC infections (3% of 369) were diagnosed during the 6-month period after the date of eligible CD4 cell count. Median time to MAC diagnosis for these 11 patients was 62 days (IQR 43–126, maximum 139 days). Ten infections were diagnosed during 1996–2003, and one during 2007. MAC infections were observed only among patients who had viral load > 1000 copies/mL at the time of qualifying CD4 cell count, but the differences in the MAC incidence were not statistically different (overlapping 95% CIs) for patients with different baseline viral load levels (Table 1).

The overall rate of MAC infections was rate = 0.6/100 pmos. Four infections were observed among the 175 patients (rate = 0.4/100 pmos) prescribed MAC prophylaxis. Seven infections were observed among the 194 patients (rate = 0.7/100 pmos) not prescribed MAC prophylaxis. These rates did not differ significantly (Fisher exact test, $p = 0.644$) (Table 1).

We also did not detect any statistically significant differences in the rate of MAC by age (0.7/100 pmos among patients < 35 years old and 35–44 years old vs. 0.3/100 pmos among patients > 45 years old, $p = 0.42$, 0.37 , respectively), sex (0.8/100 pmos among females vs. 0.5/100 pmos among males, $p = 0.51$), race/ethnicity [0.4/100 pmos among non-Hispanic whites vs. 0.5/100 pmos among non-Hispanic blacks ($p = 0.074$), vs. 1.2 /100 pmos among all other race/ ethnicities ($p = 0.19$)], or type of insurance (0.8/100 pmos among publically insured vs. 0.3/100 pmos privately insured patients, $p = 0.22$).

Discussion

In our study of 369 patients, no MAC infections were observed among the 71 patients who were virologically suppressed (< 1000 copies/mL) at the time of eligible CD4 cell count, regardless of whether they were or were not prescribed MAC prophylaxis. The low rates of MAC infection in patients with HIV RNA plasma viral loads < 10,000 copies/ mL did not differ significantly whether or not MAC prophylaxis was prescribed. These findings suggest that primary MAC prophylaxis may not be required among patients receiving cART and who are virologically suppressed. Eliminating primary MAC prophylaxis could reduce healthcare costs, reduce pill burden, and reduce the risk of drug–drug interactions and adverse treatment effects.¹²

Since the advent of the cART era, MAC infection rates have remained durably low in the large HOPS cohort studied.⁴ The small number of MAC infections (11 out of 369) we observed were concentrated in the period between 1996–2003 with only one in 2007, consistent with the decline in opportunistic infection incidence associated with the advent of potent cART.⁴ The extremely low incidence of MAC even in patients with advanced HIV disease and profound immunosuppression in the era of cART is notable. Environmental exposures and genetic factors may contribute to the existence of those few remaining MAC cases.¹³

Our study is subject to some limitations associated with medical chart abstraction study and a small number of cases resulting in low statistical power. First, in the context of widespread cART treatment, it is possible that the additional effect size associated with prophylaxis in reducing the rates of already rare MAC events was too small for us to detect statistically, a problem shared by other studies of MAC incidence in the cART era.⁴ The effectiveness of MAC prophylaxis in persons with low CD4 cell counts has been established in randomized clinical trials performed before introduction of cART.¹⁴ More recently, a study performed by Brooks and colleagues¹⁵ found that, among HIV-infected patients followed in the Adult and Adolescent Spectrum of Disease Project who had *nadir* CD4 cell counts < 50 cells/ μ L and access to cART as per prevailing guidelines, MAC incidence was below 25 infections per 1000 person years (py) of observation during 2000–2002 as compared with about 150 infections per 1000 py during 1993–1995.¹⁵ Our estimates of overall MAC incidence of 0.6/100 pmos, (equivalent to 67 per 1,000 py) *within 6 months of documented CD4 cell count < 50 cells/ μ L* during 1996–2007 therefore fall in the expected range. Second, we did not have information on patient adherence to cART or MAC prophylaxis, which complicates inferences about the effectiveness of MAC prophylaxis. Last, although data in the HOPS are collected prospectively, the data are subject to routine limitations of chart abstraction, where

information recorded in charts may incompletely capture patient's experience, such as prescription of prophylaxis or care for MAC infections at facilities outside the providers' catchment.

In summary, our observational data suggest that primary MAC prophylaxis may not be required for virologically suppressed patients receiving cART. Ideally, larger studies and randomized controlled trials are needed to confirm our findings. However, studies of such magnitude may not now be possible due to the low incidence of MAC in the cART era.

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Table 1

Incident *Mycobacterium avium* Complex (MAC) Infection Rate Among 369 Patients Eligible for MAC Prophylaxis While Prescribed cART, by Proximal HIV Viral Load, the HIV Outpatient Study, 1996–2007

Viral load ^a (copies/mL)	MAC PX	N	Incident infection, n	Within 6 months of eligible CD4 + cell count			Exact 95% CI
				Person months of observation	Incident MAC rate/100 pmos	Exact 95% CI	
All		369	11	1947.87	0.56	0.30–0.98	
All	No	194	7	1013.34	0.69	0.30–1.4	
All	Yes	175	4	934.52	0.43	0.14–1.0	
< 1000	No	41	0	219.93	0.00	NE	
< 1000	Yes	30	0	178.26	0.00	NE	
1000–9999	No	15	1	77.93	1.28	0.06–6.3	
1000–9999	Yes	16	2	80.62	2.48	0.42–8.2	
10,000	No	120	6	627.57	0.96	0.39–2.0	
10,000	Yes	120	1	632.59	0.16	0.01–0.78	
Unknown	No	18	0	87.9	0.00	NE	
Unknown	Yes	9	1	43.05	2.32	0.12–11.5	

^a HIV RNA plasma viral load measured closest within 180 days prior to through 30 days after eligible CD4 cell count.

NE, not estimated because of zero events; pmos person-months of observation; PX, prescribed prophylaxis.