Incidence, Long-Term Outcomes, and Healthcare Utilization of Patients With Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome and Disseminated *Mycobacterium avium* Complex From 1992–2015

Lauren F. Collins,1 Meredith E. Clement,2,3 and Jason E. Stout2

1Department of Internal Medicine, Duke University Medical Center, Durham, North Carolina; 2Division of Infectious Diseases, Duke University, Durham, North Carolina; 3Duke Clinical Research Institute, Durham, North Carolina

**Background.** Despite the advent of combination antiretroviral therapy (cART), patients with human immunodeficiency virus (HIV) continue to develop late-stage complications including acquired immune deficiency syndrome (AIDS), disseminated *Mycobacterium avium* complex (DMAC), and death.

**Methods.** We performed an observational retrospective cohort study of HIV-infected adults who developed DMAC in the Duke University Health System from 1992 to 2015 to determine the incidence, long-term outcomes, and healthcare utilization of this population at high risk for poor outcomes. Findings were stratified by the “pre-cART” era (before January 1, 1996) and “post-cART” thereafter.

**Results.** We identified 330 adult HIV-infected patients newly diagnosed with DMAC, the majority (75.2%) of whom were male and non-Hispanic black (69.1%), with median age of 37 years. Incidence of DMAC declined significantly from 65.3/1000 in 1992 to 2.0/1000 in 2015, and the proportion of females and non-Hispanic blacks was significantly higher in the post-cART era. The standardized mortality ratios for DMAC patients who received cART were 69, 58, 27, 5.9, and 6.8 at years 1–5, respectively, after DMAC diagnosis. For patients diagnosed with DMAC in 2000 or later (n = 135), 20% were newly diagnosed with HIV in the 3 months preceding presentation with DMAC. Those with established HIV had a median time from HIV diagnosis to DMAC diagnosis of 7 years and were more likely to be black, rehospitalized in the 6 months after DMAC diagnosis, and die in the long term.

**Conclusions.** Disseminated *Mycobacterium avium* complex continues to be a lethal diagnosis in the cART era, disproportionately affects minority populations, and reflects both delayed entry into care and failure to consistently engage care.

**Keywords.** acquired immune deficiency syndrome; antiretroviral therapy; health disparities; human immunodeficiency virus; *Mycobacterium avium* complex.
Our objectives were to describe the incidence of DMAC over time, long-term outcomes, and healthcare utilization of our cohort of HIV-infected patients at Duke University Health System presenting with DMAC from 1992 to 2015. A better understanding of the epidemiology, natural history, and pattern of hospitalizations of these high-need, high-cost patients [14] with HIV/AIDS is key for designing interventions to engage this population at high risk for poor outcomes.

METHODS

Study Population

We performed an observational retrospective cohort study of HIV-infected adult patients presenting with DMAC that included all patients initially diagnosed at our center. Subjects age 18 and older presenting to Duke University Health System between January 1, 1992 and June 30, 2015 with DMAC were ascertained using an existing research database (for patients presenting 1992–1999) and the Duke Enterprise Data Unified Content Explorer (DEDUCE) research tool (for patients presenting 2000–2015). The DEDUCE is an interface used to extract data from the electronic medical record [15].

Data Procurement

The existing research database (for patients presenting 1992–1999) was constructed in the early 2000s by searching for “Mycobacterium avium complex” (MAC) in the Duke University microbiology culture records and then building a clinical database by manual chart review of all patients with positive culture results. The clinical database included demographic information, HIV status (defined below), laboratory and radiographic data, and treatment regimens for both DMAC and HIV/AIDS if applicable. For patients presenting 2000–2015, subjects were ascertained by searching for the International Classification of Diseases, Ninth Revision code 031.2 via the DEDUCE research tool and then confirming culture positivity for DMAC and virologic or serologic evidence of HIV by manual chart review (see definition below). Persons with a diagnosis of HIV/AIDS-DMAC had data extracted from DEDUCE including demographic, clinical, and microbiological variables. Additional review of the electronic medical record was performed to extract diagnostic, treatment, and outcome data for patients presenting 2000–2015.

Disseminated Mycobacterium avium Complex Incidence, Epidemiology, and Long-Term Outcomes

To determine the incidence of DMAC in patients with HIV presenting for care at Duke from 1992 to 2015, HIV clinic census data were obtained from institutional administrative reports and DEDUCE searches. To evaluate the epidemiology and long-term outcomes of patients with HIV/AIDS who developed DMAC before and after the availability of cART, the following data elements were extracted from both research tools (the existing clinical database and DEDUCE) and supplemented by manual chart review: patient age, gender, race/ethnicity, timing of cART initiation in relation to DMAC diagnosis (if applicable), presence of other OIs, and development of immune reconstitution inflammatory syndrome (IRIS). For patients presenting 2000–2015, mortality data were obtained from DEDUCE as well as by review of the electronic medical record, and for those presenting 1992–1999, mortality data were obtained by manual chart review. For patients not known to be deceased, survival was censored either at the most recent visit to the Duke University Health System or June 30, 2015, whichever was earlier.

Timing of Human Immunodeficiency Virus Diagnosis and Hospitalization Patterns

For patients with HIV presenting to the Duke University Health System from 2000 to 2015, DEDUCE allowed for capture of additional data elements to study the timing of HIV diagnosis in relation to the diagnosis of DMAC and the hospitalization pattern of patients with HIV/AIDS who developed DMAC. The number of hospitalizations and associated admission diagnoses were recorded for all patients with HIV/AIDS-DMAC in the year before and 2 years after first positive sterile culture for DMAC.

Definitions

A diagnosis of DMAC was defined as (1) confirmed diagnosis of HIV infection plus (2) a positive culture for Mycobacterium avium complex from blood, bone marrow, or biopsy of a sterile site. Patients with positive cultures only from nonsterile sites such as sputum, stool, or bronchoalveolar lavage were excluded from the cohort. Human immunodeficiency virus diagnosis was confirmed by positive HIV-1 antibody testing or viral load. The date of DMAC diagnosis was defined by the date on which the first diagnostic specimen that grew MAC was obtained. A “new” diagnosis of HIV was defined as documentation of HIV initially diagnosed within the 3 months before DMAC presentation.

The “pre-cART era” was defined as before January 1, 1996, and the “cART era” was defined as January 1, 1996 or later. Combination antiretroviral therapy was defined by an antiretroviral regimen that included (1) a protease inhibitor plus 2 nucleoside reverse-transcriptase inhibitors, (2) a nonnucleoside reverse-transcriptase inhibitor plus 2 nucleoside reverse-transcriptase inhibitors, (3) an integrase inhibitor plus 2 nucleoside reverse-transcriptase inhibitors, or (4) an integrase inhibitor plus a boosted protease inhibitor. Human immunodeficiency virus-associated OIs were defined using the Centers for Disease Control and Prevention criteria [16]. Immune reconstitution inflammatory syndrome was defined by clinical manifestations of inflammation after initiation of cART, with pretreatment CD4 count <200 cells/mm and positive virologic and/or immunologic response to cART.
Statistical Analysis
The annual incidence of DMAC was calculated using the number of newly diagnosed DMAC patients as the numerator and the population of patients with HIV seen at least once in the Duke Adult Infectious Diseases Clinic during the same year as the denominator. Survival was measured using the Kaplan-Meier method. Differences in survival among groups were assessed using Cox proportional hazard modeling. A standardized mortality curve was constructed using US life expectancy tables (available at http://www.cdc.gov/nchs/fastats/life-expectancy.htm) for a cohort of the same age, gender, and race/ethnicity composition as the DMAC patient cohort. Differences in continuous variables were assessed using the Wilcoxon rank-sum test, and differences in categorical variables were assessed using the $\chi^2$ or Fisher’s exact test, as appropriate. Statistical analysis was performed with R version 3.2.3 (R Core Team [2016]).

Human Subjects
This retrospective record review was deemed minimum risk and approved by the Duke University Medical Center Institutional Review Board.

RESULTS
We identified 330 adult HIV-infected patients newly diagnosed with DMAC in the Duke University Health System from 1992 to 2015. The majority of patients were male (75.2%) and non-Hispanic black (69.1%), with a median age of 37 years (interquartile range [IQR] = 31–43 years, range 19–71) as shown in Table 1. The median age of patients was approximately the same in the pre-cART compared with cART era, although the proportion of females (18.4% versus 29.6%, $P = .03$) and non-Hispanic blacks (55.3% versus 79.4%, $P < .001$) was significantly higher in the cART era (Table 1).

The incidence of DMAC in HIV-infected patients declined from a peak of 65.3/1000 in 1992 to 2.0/1000 in 2015 (Figure 1). More than half of the total cohort of patients (54.8%) was never started on cART, including 46 of the 189 patients (24.3%) diagnosed in the post-cART era (Table 1). A minority of individuals diagnosed with DMAC before the availability of cART (4.3%) survived long enough to start this therapy. Of the 57 of 189 patients in the cART era who were initiated on cART after presentation with DMAC, more than half (53.4%) were prescribed antiretroviral therapy within 30 days after DMAC diagnosis. Of all patients prescribed cART, IRIS occurred in 26 of 150 (17.3%) of patients newly diagnosed with DMAC.

Median follow-up time after DMAC diagnosis was 259 days (IQR = 82–581 days, range 0–7544), resulting in 679 total patient-years of follow-up. Median survival was 189 days in patients who never started cART (95% confidence interval [CI], 152–255 days), but the median survival was not reached (60% still alive at median follow-up time of 454 days) among patients who received cART (Figure 2A). Of patients who ever received cART, 37 of 150 (25%) were known to be alive at 5 years post-DMAC and 10 (7%) were alive at 10 years post-DMAC diagnosis. To put this in context, the expected mortality of a cohort of the same age, gender, and racial/ethnic makeup in the general US population would be approximately 1.5% over 5 years; the standardized mortality ratios for all DMAC patients who received cART ($n = 144$; 6 patients of Asian, Native American, or unknown race, for whom life tables were not available, were excluded for this analysis) were 69 (95% CI, 42–94), 58 (95% CI, 44–70), 27 (95% CI, 21–33), 5.9 (95% CI, 4.5–7.3), and 6.8 (95% CI, 4.8–8.7) at years 1–5, respectively, after DMAC diagnosis. In contrast, standardized mortality ratios for patients who never

### Table 1. Clinical and Demographic Characteristics of Patients With HIV/AIDS and Disseminated Mycobacterium avium Complex Infection From 1992 to 2015

| Characteristic | Pre-cART Era ($n = 141$) | cART Era ($n = 189$) | $P$ Value |
|---------------|-------------------------|----------------------|-----------|
| Age (median, range) | 36 (19–55) | 38 (22–71) | .06 |
| %Female | 18.4% | 29.6% | .03 |
| Race/ethnicity | | | |<.001 |
| Black, non-Hispanic | 78 (55.3%) | 150 (79.4%) | |
| White, non-Hispanic | 61 (43.3%) | 27 (14.3%) | |
| Hispanic | 0 (0%) | 5 (2.6%) | |
| Native American | 1 (0.7%) | 2 (1.1%) | |
| Asian | 1 (0.7%) | 1 (0.5%) | |
| Unknown | 0 (0%) | 4 (2.1%) | |
| Antiretroviral therapy (at the time of DMAC diagnosis) | | (not relevant) | |
| Never received | 135 (95.7%) | 46 (24.3%) | |
| Already prescribed | 0 (0%) | 83 (43.9%) | |
| Started within 30 days | 0 (0%) | 31 (16.4%) | |
| Started within 31–180 days | 0 (0%) | 17 (9.0%) | |
| Started >180 days | 6 (4.3%) | 9 (4.8%) | |
| Unknown | 0 (0%) | 3 (1.6%) | |

Abbreviations: AIDS, acquired immunodeficiency syndrome; cART, combination antiretroviral therapy; DMAC, disseminated Mycobacterium avium complex; HIV, human immunodeficiency virus.
received cART were 275 (95% CI, 245–298), 280 (95% CI, 246–303), 236 (95% CI, 167–278), 0 (95% CI, 0–283), and 99 (95% CI, 41–143) at years 1–5 (the standardized mortality ratio for year 4 is 0 because none of the 4 patients living at the start of year 4 died that year).

Additional data were available from the DEDUCE system for HIV-infected patients diagnosed with DMAC in 2000 or later (n = 135). At the time of presentation of DMAC, 10 of 135 (7%) patients were unaware of their HIV diagnosis, and an additional 18 (13%) had been newly diagnosed with HIV in the prior 3 months. Table 2 compares patients newly diagnosed with HIV (n = 28) to patients with an established HIV diagnosis (n = 107). Patients with an established HIV diagnosis had a median time from HIV diagnosis to DMAC diagnosis of 7 years (IQR = 4–10 years, range 4 months–22 years). Those with longstanding HIV at the time of DMAC presentation, compared with their newly diagnosed counterparts, were more likely to be black (84% vs 64%, P = .008) and more likely to have never started cART (18% vs 4%, P < .001) as shown in Table 2. Survival was not significantly different (log-rank P = .39) between newly diagnosed and established patients overall, but the survival curves diverge at approximately the first year after DMAC diagnosis, with continued mortality in the established patient group but no further deaths in the newly diagnosed group (Figure 2B).

Figure 3 illustrates the pattern of hospitalization for a period spanning the year before DMAC diagnosis to 2 years after DMAC diagnosis, stratified by timing of HIV diagnosis. Hospitalization both before and after DMAC diagnosis was common; however, persons newly diagnosed with HIV had fewer hospitalizations overall compared with those known to have HIV for at least 3 months before DMAC diagnosis. Of note, 1 patient was admitted twice to the hospital within the year before DMAC diagnosis but was not diagnosed with HIV until 10 days before DMAC diagnosis and died less than 1 month after DMAC diagnosis.
The majority of patients with DMAC (59%) were rehospitalized in the 6 months after DMAC diagnosis (median 1 hospitalization, IQR = 0–2, range 0–8); another 42% of those still alive at 7 months after DMAC diagnosis were also hospitalized between 7 and 12 months after DMAC diagnosis (median number of hospitalizations 0, IQR = 0–1.8, range 0–7). Patients with newly diagnosed HIV were less likely to be rehospitalized in the 6 months after DMAC diagnosis (10 of 28, 36%) than patients with HIV status known for at least 3 months before DMAC diagnosis (69 of 107, 64%, P = .011 for comparison).

**DISCUSSION**

We describe the incidence, epidemiology, long-term outcomes, and healthcare utilization of patients with HIV/AIDS who develop DMAC in the cART era. Our study is novel in that (1) few studies in the cART era have focused specifically on DMAC [11–13], (2) we report on a prolonged observation period (>20 years), and (3) hospitalization patterns in a population of HIV/AIDS-DMAC patients have not previously been described. We found that although incidence has significantly decreased since the advent of cART, DMAC continues to be a lethal diagnosis for patients with HIV, disproportionately afflicts minority populations, and reflects both delayed entry into care and failure to consistently engage in care. Furthermore, frequent hospital utilization by this medico-psychosocially complex patient group highlights the need for individual- and systems-based interventions to improve care delivery and engagement for this high-need, high-cost population [14] at substantial risk of poor outcomes.

We found the incidence of DMAC has dramatically declined since the advent of cART in 1996 and has approximately stabilized since 2005. This finding is consistent with multicohort analyses of AIDS-defining OIs in North America [6, 17], which highlight DMAC as one of the most common OIs before and after the availability of cART. Corroborating prior studies [11, 12], we demonstrated that the proportion of females (18.4% versus 29.5%) and non-Hispanic blacks (55.3% versus 79.5%) was significantly higher in the cART era. This underscores the persistence over time of racial/ethnic and gender disparities in HIV care, with black persons being particularly vulnerable to such inequality [18, 19]. Factors associated with disparities in antiretroviral therapy prescription and viral suppression differ for men and women of the same race/ethnicity [19], suggesting that gender—in addition to race—contributes to inequity in access and outcomes along the HIV care continuum.

Success across the multistep “HIV treatment cascade” from timing of diagnosis to virologic suppression [20–22] is severely challenged for patients with HIV who develop DMAC. We identify 2 distinct populations of patients who experience breakdown in this cascade at varying points: (1) those with significantly delayed entry into care who are newly diagnosed with HIV near the time of presentation with DMAC, and (2) those with longstanding known HIV who fail to consistently engage in care and ultimately develop late-stage complications of AIDS, such as DMAC. Our data suggest that these groups are slightly different; in our cohort, patients with an established HIV diagnosis who presented with DMAC were more likely to be black, more likely to never initiate antiretroviral therapy, more likely to be rehospitalized in the 6 months after DMAC diagnosis, and more likely to die in the long term than patients newly diagnosed with HIV. This dramatically divergent “natural history” of patients with known HIV that is longstanding—often on the order of several years—who nevertheless fail to engage in...
Conclusions

In conclusion, although the incidence of DMAC in persons with HIV infection has diminished over time, patients who receive a diagnosis in the post-cART era remain at high risk for complications and recurrent hospitalizations. Disseminated *Mycobacterium avium* complex is a late-stage OI that increasingly and disproportionately afflicts racial minorities, reflecting both trends in HIV epidemiology in the United States as well as...
delays in access to care among minority groups. Patients with HIV who develop DMAC are at very high risk for death and hospitalization for several years after diagnosis. Encouragingly, we demonstrate that long-term survival may be achieved with cART, even for patients with delayed presentation to care and/or those who fail to engage in care. Continued prioritization of strategy development and implementation to link and engage this medico-behaviorally complex population of patients in HIV care is critically needed.

Acknowledgments

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Financial support. This research was funded by a Faculty-Resident research grant from Duke University Department of Medicine (to L. E. C.) and by the National Institutes of Health under award number 5T32AI007392-25 (to M. E. C.).

Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Nakagawa F, May M, Phillips A. Life expectancy living with HIV: recent estimates and future implications. Curr Opin Infect Dis 2013; 26:17–25.
2. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One 2013; 8:e81355.
3. Rodger AJ, Lodwick R, Schechter M, et al. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. AIDS 2013; 27:973–9.
4. Moore RD, Keruly JC, Bartlett JG. Improvement in the health of HIV-infected persons in care: reducing disparities. Clin Infect Dis 2012; 55:1242–51.
5. Wada N, Jacobson LP, Cohen M, et al. Cause-specific life expectancies after hospitalization for several years after diagnosis. Encouragingly, HIV who develop DMAC are at very high risk for death and hospitalization for several years after diagnosis. Continued prioritization of strategy development and implementation to link and engage this medico-behaviorally complex population of patients in HIV care is critically needed.

16. Schneider E, Whitmore S, Glyn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years—United States, 2008. MMWR Recomm Rep 2008; 57:1–12.
17. Buchacz K, Baker RK, Pallola FJ Jr, et al. AIDS-defining opportunistic illnesses in US patients, 1994–2007: a cohort study. AIDS 2010; 24:1549–59.
18. Beer L, Bradley H, Mattson CL, et al. Trends in racial and ethnic disparities in antiretroviral therapy prescription and viral suppression in the United States, 2000-2013. J Acquir Immune Defic Syndr 2016; 73:466–53.
19. Beer L, Mattson CL, Bradley H, Skarbinski J. Understanding cross-sectional racial, ethnic, and gender disparities in antiretroviral use and viral suppression among HIV patients in the United States. Medicine (Baltimore) 2016; 95:e171.
20. Gardner EM, McLees MP, Steiner JF, et al. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis 2011; 52:793–800.
21. Mugavero MJ, Amico KR, Horn T, Thompson MA. The state of engagement in HIV care in the United States: from cascade to continuum to control. Clin Infect Dis 2012; 55:1164–71.
22. Centers for Disease Prevention and Control. HIV in the United States: The Stages of Care. CDC Fact Sheet. 2012. Available at: https://www.cdc.gov/hiv/pdf/research_stagesofcare.pdf. Accessed 1 May 2017.
23. Lima VD, Hogg RS, Harrigan PR, et al. Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. AIDS 2007; 21:685–92.
24. Bonnet F, Lewden C, May T, et al. Opportunistic infections as causes of death in HIV-infected patients in the HAART era in France. Scand J Infect Dis 2005; 37:482–7.
25. Ingle SM, May MT, Gill MJ, et al. Impact of risk factors for specific causes of death in the first and subsequent years of antiretroviral therapy among HIV-infected patients. Clin Infect Dis 2014; 59:287–97.
26. Pallela FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006; 43:27–34.
27. Djawe K, Buchacz K, Hsu L, et al. Mortality risk after AIDS-defining opportunistic illness among HIV-infected persons—San Francisco, 1981–2012. J Infect Dis 2015; 213:1166–75.
28. Simard EP, Fransua M, Naishadham D, Jemal A. The influence of sex, race/ethnicity, and educational attainment on human immunodeficiency virus death rates among adults, 1993–2007. Arch Intern Med 2012; 172:1591–8.
29. Antiretroviral Therapy Cohort Collaboration (ART-CC). Influence of geographical origin and ethnicity on mortality in patients on antiretroviral therapy in Canada, Europe, and the United States. Clin Infect Dis 2013; 56:1800–9.
30. Buchacz K, Baker RK, Moorman AC, et al. Rates of hospitalizations and associated diagnoses in a large multisite cohort of HIV patients in the United States, 1994–2005. AIDS 2008; 22:1345–54.
31. Hellinger FJ. The changing pattern of hospital care for persons living with HIV: 2000 through 2004. J Acquir Immune Defic Syndr 2007; 45:239–46.
32. Yehia BR, Fleshman JA, Hicks PL, et al. Inpatient health services utilization among HIV-infected adult patients in care 2002–2007. J Acquir Immune Defic Syndr 2010; 53:397–404.
33. Tai M, Liu T, Merchant RC. Hospitalizations in the United States among HIV-infected individuals in short-stay hospitals, 1982 to 2010. J Int Assoc Provid AIDS Care 2015; 14:408–14.
34. Crum-Cianflone NF, Grandits G, Echols S, et al. Trends of causes and hospitalizations among HIV-infected persons during the late HAART era: what is the impact of CD4 counts and HAART use? J Acquir Immune Defic Syndr 2010; 54:248–57.
35. Gebo KA, Diener-West M, Moore RD. Hospitalization rates in an urban cohort after the introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2001; 27:143–52.
36. Fleshman JA, Gebo KA, Reilly ED, et al. Hospital and outpatient health services utilization among HIV-infected adults in care 2000–2002. Med Care 2005; 43:1110–52.
37. Alhoff KN, Buchacz K, Hall HI, et al. U.S. trends in antiretroviral therapy use, HIV RNA plasma viral loads, and CD4 T-lymphocyte cell counts among HIV-infected persons, 2000 to 2008. Ann Intern Med 2012; 157:325–35.
38. Hall HI, Tang T, Westfall AO, Mugavero MJ. HIV care visits and time to viral suppression, 19 U.S. jurisdictions, and implications for treatment, prevention and the national HIV/AIDS strategy. PLoS One 2013; 8:e84318.
39. Supervie V, Marty L, Lacombe JM, et al. Looking beyond the cascade of HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis 2011; 52:793–800.