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Background: Infectious diseases remain a leading cause of mortality in South Africa, compounded by a high HIV prevalence. This study aimed to delineate the spectrum and clinicopathological characteristics of fatal infectious diseases through a postmortem audit to inform clinical practice and public health strategy. **Methods:** A retrospective, cross-sectional descriptive study was conducted on all autopsies with a final cause of death attributed to infectious disease at a national laboratory in Gauteng, South Africa, from 2012 to 2021. Using the Systematised Nomenclature of Medicine Clinical Terms (SNOMED) code and word search engines codes, 55 cases were identified. Data on demographics, clinical presentation, HIV status, antiretroviral therapy (ART), comorbidities, and final autopsy diagnosis were extracted from the laboratory information system. Histological confirmation was performed using standard stains. Descriptive statistical analysis was conducted using STATA-18. **Results:** The cohort (n=55) had a median age of 32.6 years (IQR 19.0–45.5) and was predominantly female (67.3%). HIV prevalence was 34.6% (n=19), with 68.4% of those on ART. The leading cause of death was multilobar pneumonia (36.6%), followed by bronchopneumonia (21.8%). AIDS-defining illnesses were present in 27.3% of cases, with disseminated tuberculosis being the most common (50% of these). Septic shock was identified in 18.2% of decedents. A significant proportion (70.9%) of the cohort was HIV-negative. **Conclusions:** This autopsy series reveals a high burden of fatal community-acquired pneumonias and HIV-associated opportunistic infections, with a notable proportion of deaths occurring in HIV-negative individuals. The findings underscore diagnostic gaps and highlight the critical role of autopsy in accurate mortality surveillance, advocating for enhanced antemortem diagnostic protocols and targeted public health interventions.

Keywords: Prevalence, autopsy, infections, HIV/AIDS