Objective: Our aim was to define the impact of co-morbidities on the prognosis of HIV-positive patients with relapsed/refractory lymphoma (RRL) after first-line chemotherapy. Methods: From January 2001 to July 2012 we collected data of 74 unselected HIV-positive patients (23 HL and 51 NHL) with RRL. We checked the prognostic impact of some indexes: HIV score, aa-IPI score, HCT-CI and disease chemosensitivity. HCT-CI, proposed by Sorror and colleagues for allogeneic hematopoietic cell transplantation (HCT), was extended as a tool to assess the role of co-morbidities in HIV-positive population. We defined a chemosensitive disease a RRL in which at least a partial remission was obtained after salvage treatment. Results: Mild and moderate/severe hepatic impairment (in 28 and 19 patients, respectively) and moderate and severe pulmonary disturbances (in 27 and 16 patients, respectively), were the most commonly encountered co-morbidities. At the time of multivariate analysis the OS and PFS were influenced significantly only by disease chemosensitivity whereas non-relapse mortality was significantly affected only by HCT-CI index. OS (69% versus 5%) and PFS (51% versus 10%) at 5 years were significantly better for HIV-positive patients submitted to autologous HCT than those who did not receive it. Conclusions: Our data should lead us to recognize the burden of co-morbidities affecting HIV-positive patients clinical history. HTC-CI index may help to identify the mortality risk due to treatment toxicity also in the HIV-positive population. Intensive chemotherapy, including autologous HCT, may be deserved only to HIV-positive patients affected by RRL in whom the role of co-morbidities is marginal.