Allogeneic stem cell transplantation alone is unlikely to provide the HIV-1 cure

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Despite the great success in the development of effective combination antiretroviral therapy, and the transformation of a once universally fatal infection into a manageable chronic condition, there remains no ‘cure’ for HIV-1 infection. This is remarkable, but not surprising. Remarkable because, despite the tens of millions of people historically and currently infected with HIV-1, to date there has been just one *bona fide* case of HIV-1 cure [1]. Not surprising though, due to the integration of the virus into the host genome, the resistance of infected cells to cell death [2] and the persistence and stability of the latent viral reservoir [3] which is unaffected by current antiretroviral medications.

It is natural, then, to question why the cure of ‘Berlin patient’ occurred in the first place, and whether this singular event could be recapitulated. That one cure occurred within the context of several rare events: myeloablative chemotherapy for a hematologic malignancy (acute myelogenous leukemia); two successive allogeneic stem cell transplantations from a donor homozygous for the protective *CCR5*Δ32 mutation rendering the allograft cells resistant to HIV-1 infection; and subsequent graft versus host disease (GVHD). Since intentionally repeating all three of these events in another patient would be virtually impossible and unnecessarily risky compared with suppressive antiretroviral therapy alone, it is reasonable then to ask if any one of these events might provide another HIV-1 cure.

Worldwide clinical experience treating malignancies in HIV-1 positive patients with a broad range of cytotoxic chemotherapeutic agents over several decades has failed to cure any other patient of HIV-1. However, newer antineoplastic agents are being repurposed in the search for a HIV-1 cure, including histone deacetylase inhibitors to reactivate latent HIV-1 and immune checkpoint inhibitors, among others [4]. We have recently shown that treatment of *ex vivo* CD4 T cells from HIV-1 positive patients with venetoclax, a BCL-2 specific inhibitor which is FDA-approved for the treatment of chronic lymphocytic leukemia, reduces HIV-1 reservoir size by sensitizing infected cells to HIV-induced apoptosis [5].

We, and others, have reported additional cases of allogeneic stem cell transplantation which were associated with reduced HIV-1 reservoir size, but ultimately without HIV-1 cure, suggesting that allogeneic transplantation is insufficient [6–8]. Notably, these cases involved donors with wild type *CCR5*. However, co-receptor tropism switch and viral escape of *CCR5*Δ32 selection in stem cell transplantation have been reported, suggesting modulation of *CCR5* expression is also not sufficient for HIV-1 cure [9]. Furthermore, there is currently no reliable biomarker of HIV-1 reservoir size that is sensitive enough to adequately predict HIV-1 cure [10,11]. In fact, in the cases referenced above, multiple independent measures of HIV-1 were at or below the limit of detection, similar to the ‘Berlin patient’ [12] and yet viral rebound occurred.

Finally, our recent data [8] suggest that clinical GVHD may not have a graft versus HIV effect as previously hypothesized. In our reported patient, clinical GVHD was associated with increased expression of immune activation markers on a number of immune cell types, and occurred coincidentally with evidence of clonal expansion of latent

HIV-1 sequences. Therefore, GVHD may induce homeostatic proliferation and persistence of cells containing latent HIV-1, rather than immune-mediated clearance of residual recipient-derived cells.

Therefore, it is unlikely that allogeneic stem cell transplantation alone could provide a method for HIV-1 cure, at least at a success rate and cost that would justify the significant attendant risks. However, it still remains an important area to investigate, as few if any other treatments have been shown to reduce the HIV-1 reservoir size to any degree. Important questions remain, including: effects of different conditioning regimens on pre-transplant reservoir size; effects of donor and recipient genetic mutations other than *CCR5* on changes in reservoir size after transplant; the role of extra lymphoid tissue HIV-1 reservoirs in viral persistence and relapse; the potential role of prophylactic or therapeutic HIV-1 vaccination after transplantation to boost anti-HIV immunity in an otherwise naïve immune system; and the role of immune activation from GVHD or opportunistic infections in promoting viral persistence.

The idea that a single ‘magic bullet’ intervention will result in an HIV-1 cure has largely been abandoned. However, careful and systematic observation of HIV-1 positive individuals who are undergoing allogeneic stem cell transplantation for another reason, such as a hematologic malignancy, may identify combinations of interventions that lead to substantial reductions in HIV-1 reservoir size, and thereby lead to new insights and novel targets for a potential future multimodality HIV-1 cure.

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