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Risks and Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies in Patients with HIV Infection

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Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative therapy for hematologic malignancies in persons living with HIV (PLHIV), however, uncertainties exist in many domains related to their care, including optimal donor selection, conditioning regimen, immunosuppression for graft-versus-host disease (GVHD), and long-term outcomes. We undertook a comprehensive systematic review from multiple databases to evaluate the foregoing uncertainties. The final sample comprised 49 patients (median age at HCT, 34 years; 46 males [93.8%]). Acute GVHD (aGVHD) was reported in 19 patients (59.3%) in the overall cohort, with grade II in 12 (37.5%) and grade III in 2 (6.2%). In the entire cohort, overall survival (OS) was 81.6% at 6 months and 56.6% at 12 months. Among 32 patients, the OS at 6 months was 73.3% for patients who received myeloablative conditioning (MAC) and 88.2% for those who received reduced-intensity conditioning (RIC), and OS at 12 months was 53.3% for MAC and 58.8% for RIC. Twenty-four patients were alive in complete remission on long-term follow-up, with 25 deaths reported. Fifteen deaths (60%) occurred due to relapse, including 3 (12%) from infection, 2 (8%) from GVHD, and 5 (20%) from other causes, including renal failure, respiratory failure, and liver failure. To our knowledge, this is the largest series of allo-HCT in PLHIV reported to date, and our results indicate that clinical outcomes (including engraftment, infection rate, and survival) are not significantly different from those in patients without HIV (historical controls). RIC regimens are associated with a slightly greater likelihood of survival compared with MAC regimens. Prospective trials are critically needed to evaluate the optimal conditioning regimens, ideal donor source, and most appropriate GVHD prophylaxis.

INTRODUCTION

The worldwide prevalence of HIV is approximately 37 million, and antiretroviral therapy (ART) has considerably improved survival in HIV-infected patients, with dramatic declines in morbidity and mortality since its introduction [1–3]. Despite these improvements, approximately 1 million HIV-related deaths occur annually. Despite the availability of ART, persons living with HIV (PLHIV) are at greater risk of developing both hematologic and solid organ malignancies compared with the general population [4]. Among these hematologic malignancies include not only the so-called "AIDS-defining" malignancies like non-Hodgkin lymphomas (diffuse large B-cell lymphoma [DLBCL], Burkitt lymphoma, and primary lymphomas of the central nervous system), but also other hematologic malignancies, including T cell lymphomas, Hodgkin lymphoma, leukemias, and multiple myeloma [5–8]. Although the risk of AIDS-defining non-Hodgkin lymphomas has decreased among PLHIV in developed countries secondary to the wide availability and effectiveness of ART, the risk still remains higher than that in the general population [7].

The increased risk of non-AIDS-defining malignancies is related to immunosuppression and dysregulated immune status, with likely chronic immune activation [7]. Risk factors for acute myelogenous leukemia (AML) in PLHIV include immunosuppression, increased incidence of myelodysplasia (MDS) and

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secondary transformation into AML, and impairment of the regulatory functions of auxiliary cells, including endothelial cells, fibroblasts, and lymphocytes [8,9]. In addition, with the improved life expectancy of PLHIV with use of ART, the prevalence of these malignancies is increasing. A French study reported a twofold increased incidence of AML in PLHIV compared with the general population [8]. A US-based study reported that 50% of the malignancies diagnosed in PLHIV were in excess of the expected rate in the general population, for a twofold greater risk of cancer in PLHIV [10].

Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative therapy for hematologic malignancies in general. There has been reluctance to use allo-HCT for HIV patients with hematologic malignancies secondary to multiple factors, including an immunosuppressed state at baseline with high risk of opportunistic infections, a possible direct effect of HIV on reconstituted donor T cells, increased conditioning regimen-related toxicities, interactions between ART and conditioning regimens and other drugs used during HCT, and delayed engraftment, resulting in increased transplantation-related mortality (TRM). This hesitancy can deprive some PLHIV with hematologic malignancies of potentially curative therapy.

There has been a significant advancement in the treatment of HIV infection, with improvements in quantitative $CD4^+$ T cell immunity, prevention and treatment of opportunistic infections, suppression of HIV replication to undetectable levels, and greater understanding of side effect profiles, drug interactions, and general tolerability. Moreover, advances in supportive care, including the availability of newer antifungal, antibiotic, and antiviral drugs for both prophylaxis and treatment have improved the outcomes of allo-HCT in general. Increasing evidence of a graft-versus-tumor effect has led to the use of nonmyeloablative (NMA) or reduced- intensity conditioning (RIC) regimens in patients in whom the use of myeloablative conditioning (MAC) regimen is not feasible, with comparable outcomes and improved TRM [11]. The cure of HIV in the Berlin patient after allo-HCT for AML from an unrelated donor with inherent resistance to HIV infection secondary to homozygous mutation of CCR5-delta 32 of the CCR5 receptor has inspired the transplantation community [12]. This has been followed by a few other cases in which such donors were available. A graft-versus-HIV effect also has been described explaining the potentially curative potential of the allograft [13]. Donors in that study were wild-type for CCR5, and recipients developed donor-derived $CD8^+$ T cells reactive against HIV epitopes [13].

In the current era, given the exponential growth in the use of HCT, many donor stem cell sources exist, including HLA-matched related donors (MRDs), HLA-matched unrelated donors (MUDs), mismatched unrelated donors, umbilical cord blood units (CBU), and haploidentical related donors: however, the optimal type of donor for allo-HCT is currently unknown in the absence of prospective data. Moreover, given the various types of conditioning regimens (MAC, RIC, and NMA), uncertainty exists regarding which regimen would yield optimal clinical outcomes, given the lack of randomized data comparing the different regimens for allo-HCT in PLHIV. Finally, different series of allo-HCT in PLHIV have reported widely ranging incidences of acute graft-versus-host-disease (aGVHD) and chronic GVHD (cGVHD), and thus the exact risks with different combinations of donors and conditioning regimens are unknown. To address these questions, we performed a comprehensive systematic review of HCT in PLHIV.

METHODS

For an electronic review of literature, we performed a Boolean search via PubMed/MEDLINE and the Cochrane Central Register for clinical trials using the key terms "allogeneic stem cell transplant," "bone marrow transplant," "hematologic malignancies," and "AML in patients with HIV." After screening case reports and series, retrospective and prospective studies reported between the years 2000 and 2017 were included in our review. To avoid publication bias, abstracts from annual meetings of professional societies associated with hematology/HCT and HIV were screened when the complete articles were available. Societies searched included the American Society of Hematology, American Society of Blood and Marrow Transplantation, American Society of Clinical Oncology, and American Academy of HIV Medicine. Mean and median values were calculated for the outcomes for which the data were available. The following variables were collected: number of patients, age, ART, type of donor, stem cell source, conditioning regimen, GVHD prophylaxis, neutrophil engraftment, infections, GVHD type, other complications, overall survival (OS), and cause of death. Analysis was performed evaluating the risks and outcomes pertaining to the allo-HCT. Endpoints included duration, interruptions, and adverse effects of ART; pretransplantation and post-transplantation $CD4^+$ T cell count and HIV viral load; neutrophil engraftment; occurrence of aGVHD and cGVHD; cytomegalovirus (CMV) reactivation; TRM; and OS at 6 and 12 months for all hematologic malignancies and AML. Inclusion criteria for the study included adults with HIV and hematologic malignancies eligible for allo-HCT. Exclusion criteria included opportunistic or disseminated infection at the time of transplantation.

RESULTS

After application of strict selection criteria, a total of 49 patients were included in the study. These included 17 patients from a recent prospective clinical trial, BMT CTN 0903 [14]. The remaining 32 patients were reported in the literature in case reports, small case series, and retrospective studies [11,13,15–26]. Forty-six patients (93.8%) were males, and the median age was 34 years (range 17 to 64 years).

The distribution of hematologic malignancies in the entire study cohort is shown in Figure 1. Of the 49 patients, 21 had AML, including 1 patient with therapy-related AML. There were 2 patients with chronic myelogenous leukemia, 4 patients with B cell acute lymphoblastic leukemia (ALL), 4 patients with MDS, 3 patients with Hodgkin lymphoma, 3 patients with DLBCL, 4 patients with Burkitt lymphoma, and 1 patient each with T cell ALL and Primary Effusion Lymphoma (PEL). There were 3 patients with non-Hodgkin lymphoma not otherwise specified and 1 patient each with plasmablastic lymphoma, large granular lymphocytic leukemia, and multiple myeloma.

The median $CD4^+$ T cell count at allo-HCT was 172 (range, 33 to 1661). HIV was undetectable before HCT in all but 5 patients. All patients were started or were already on ART before undergoing HCT. ART was continued during and after HCT except in patients with severe mucositis and/or persistent nausea who were not able to swallow pills. The increased viral loads in these patients were rapidly resuppressed when ART was restarted. HIV remained undetectable in most of the patients after HCT, with 2 patients requiring changes in antiretroviral treatment. In the prospective trial, HIV was detected in 2 of 3 patients who were mixed chimeras and none of 2 who were 100% donor chimeras.

Of the 32 patients reported between 2000 and 2016, donors included 14 MRDs (43.7%), 12 MUDs (37.5%), 3 mismatched unrelated donors (9.4%), 2 CBUs (6.2%), and 1 haploidentical donor (3.1%). The prospective trial reported in 2017 used 8/8 MRD or at least a 7/8 MUD [14]. The stem cell source in all patients was peripheral blood except in those receiving CBUs. The donor type distribution in the study cohort is shown in Figure 2. Conditioning regimens included MAC in 23 patients (47%), RIC in 18 patients (36.7%), and NMA in 8 patients (16.3%). MAC regimens included combinations of busulfan and cyclophosphamide (Bu/Cy) in 2 patients; cyclophosphamide and total body irradiation (TBI) (Cy/TBI) in 6 patients; busulfan and fludarabine (Bu/Flu) in 2 patients; and amsacrine, fludarabine,

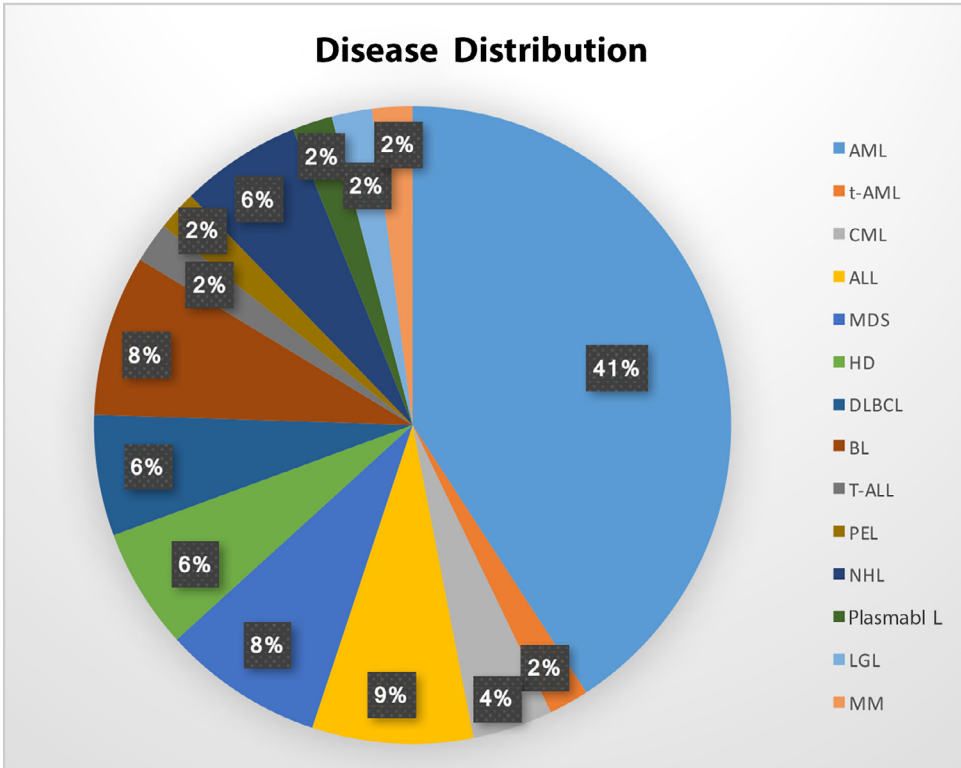

Figure 1. Disease distribution for allo-HCT in HIV-infected patients.

cytarabine, cyclophosphamide and TBI; etoposide and TBI; fludarabine, busulfan, and cyclophosphamide, busulfan and clofarabine; and rituximab with BCNU, etoposide, cytarabine, and melphalan in 1 patient each. RIC regimens included combinations of fludarabine and melphalan (Flu/Mel) in 2 patients; Bu/Flu in 3 patients; and fludarabine, cytarabine, and idarubicin; fludarabine, melphalan, and antithymocyte globulin (ATG); and Yt90, rituximab, fludarabine, and melphalan in 1 patient each. NMA conditioning regimens included combinations of fludarabine and TBI (Flu/TBI) in 5 patients, fludarabine and cyclophosphamide (Flu/Cy) in 2 patients, and fludarabine, cyclophosphamide and TBI in 1 patient. Conditioning regimens are summarized in Table 1, Figure 3. The median $CD4^+$ cell count at HCT was 172 (range, 33 to 1661). The median time to neutrophil engraftment was 17 days (range, 9 to 48 days), and the median time to platelet engraftment was 17 days (range, 14 to 31 days).

Among the 32 patients, GVHD prophylaxis included cyclosporine alone in 7, cyclosporine with methotrexate in 7,

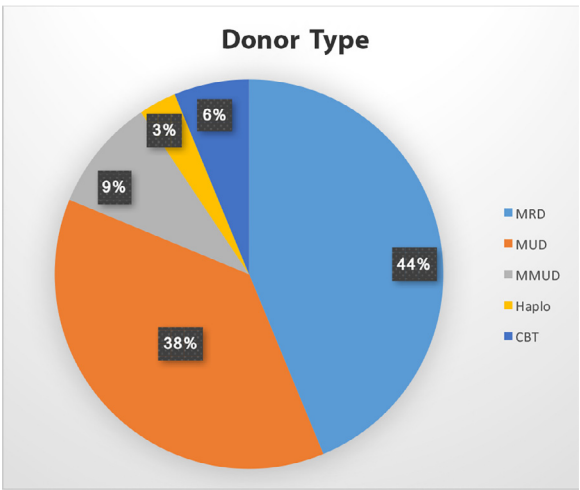

Figure 2. Donor type distribution for HCT in HIV-infected patients.

Table 1
Conditioning Regimens Used in HCT for HIV-Infected Patients

Conditioning Regimen	Number of Patients
MAC	
Busulfan and cyclophosphamide	2
Cyclophosphamide and TBI	6
Busulfan and fludarabine	2
Amsacrine, fludarabine, cytarabine, cyclophosphamide, and TBI	1
Etoposide and TBI	1
Fludarabine, busulfan, and cyclophosphamide	1
Busulfan and clofarabine	1
Rituximab with BCNU, etoposide, cytarabine, and melphalan	1
RIC	
Fludarabine and melphalan	2
Busulfan and fludarabine	3
Fludarabine, cytarabine, and idarubicin	1
Fludarabine, melphalan, and ATG	1
Yt90, rituximab, fludarabine, and melphalan	1
NMA	
Fludarabine and TBI	5
Fludarabine and cyclophosphamide	2
Fludarabine, cyclophosphamide, and TBI	1

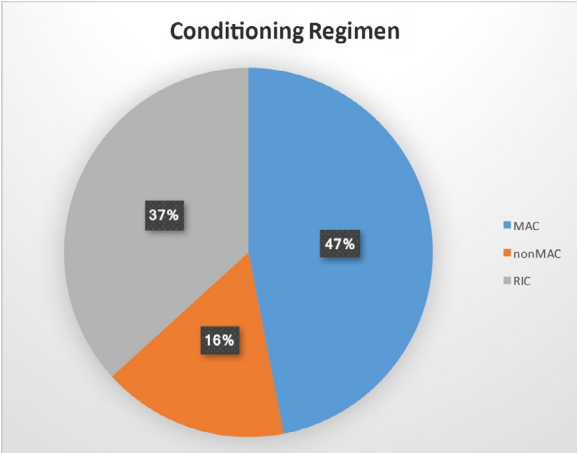

Figure 3. Conditioning regimens used for HCT in HIV-infected patients.

cyclosporine with ATG in 2, cyclosporine with mycophenolate mofetil in 4, methotrexate with tacrolimus in 3, ATG alone in 2, tacrolimus with sirolimus and methotrexate in 1, cyclosporine with steroids in 1, and post-transplantation cyclophosphamide with cyclosporine in 1. GVHD prophylaxis was not reported for 3 patients. The incidence of grade II-IV aGVHD was 41% in the 17 patients reported in a recent prospective trial [14]. aGVHD was reported in 19 (59.3%) of the 32 reported patients, with grade II in 12 patients (37.5%) and grade III in 2 patients (6.2%). No cases of grade I or IV aGVHD were reported. Six cases of cGVHD were reported among the 32 patients.

OS for all patients was 81.6% at 6 months and 56.6% at 12 months. For the 17 patients in the prospective trial, OS was 82% at 6 months and 57% at 12 months [14]. Among the other 32 patients, OS was 73.3% for those who received MAC and 88.2% for those who received NMA and RIC combined at 6 months and 53.3% for MAC and 58.8% for NMA and RIC combined at 12 months(Table 2).

For patients with AML, OS was 91.6% at 6 months and 41.6% at 12 months. In these patients, OS was 80% with MAC and 100% with NMA and RIC combined at 6 months and 40% with MAC and 42.8% with NMA and RIC combined at 12 months (Table 3). Twenty-four patients were alive in complete remission (CR) at long-term follow-up, and 25 patients died. Fifteen deaths (60%) were due to relapse, 3 (12%) were due to infection, 2 (8%) were from GVHD, and 5 (20%) were from other causes, including renal failure, acute respiratory failure, and liver failure. The causes of death are summarized in Table 4.

CMV viremia was reported in 43.7% of the patients. No cases of CMV end-organ disease were reported. In the prospective trial, the following infections were reported in 11 patients: grade 2 in 3 patients, grade 3 in 8 patients, *Escherichia coli* sepsis, pneumococcal pneumonia, multidrug-resistant *Acinetobacter baumannii* bacteremia, *Streptococcus viridans* sepsis with multiorgan failure, and *Clostridium difficile* colitis. Fungal infections included CNS toxoplasmosis, pulmonary aspergillosis, and invasive fungal pulmonary infection due to *Rhizopus*. Viral infections included BK polyomavirus cystitis, respiratory syncytial virus upper respiratory infection, norovirus gastroenteritis, and rectal herpes. Infections, including pulmonary aspergillosis and sepsis with *Pseudomonas* species and *Streptococcus* species, were responsible for 3 deaths.

Table 2
OS at 6 and 12 Months in 32 Patients Receiving MAC, NMA, RIC, and combined NMA + RIC

OS	MAC, %	NMA, %	RIC, %	NMA + RIC, %
At 6 mo (81.25%)	73.33	75.00	100	88.23
At 12 mo (56.25%)	53.33	50.00	66.66	58.82

Table 3
OS for AML in 32 patients at 6 and 12 months Receiving MAC, NMA, RIC, and combined NMA + RIC

OS	MAC, %	NMA, %	RIC, %	NMA + RIC, %
At 6 mo (91.66%)	80	100	100	100
At 12 mo (41.66%)	40	66.66	25	42.85

Table 4
Causes of Death Post-HCT for HIV-Infected Patients

Cause of Death	n (%)
Relapse	15 (60)
Infection	3(12)
GVHD	2 (8)
Acute respiratory failure	3 (12)
Renal failure	1 (4)
Liver failure	1 (4)

DISCUSSION

In this study, we evaluated 49 patients who underwent allogeneic HCT for HIV-associated hematologic malignancies using MAC or NMA/RIC in multiple institutions between 2000 and 2017. The conditioning regimens and GVHD and infection prophylaxis used in these patients were similar to those typically used in patients without HIV infection. Immune reconstitution post-HCT was comparable as well. Most of the patients had an undetectable HIV viral load at the time of transplantation. Four patients with a pretransplantation HIV viral load <1000 were continued on ART, and their viral load was undetectable on subsequent testing post-HCT. For patients who had increasing viral load secondary to peritransplantation discontinuation of ART, the viral load responded promptly to reintroduction of ART. An increasing HIV viral load at day +252 in 1 patient responded to second-line ART. We suggest that because of the risk of rebound HIV viremia, scheduled interruptions of ART during the peritransplantation period should be avoided where possible. The incidences of infectious complications, GVHD, relapse, and other complications, including mortality, in this patient population were comparable to those of their Non-HIV-infected counterparts. The case reports are summarized in Table 5, and case series are summarized in Table 6.

Reviewing the data from this largest series of HIV patients with hematologic malignancies shows that the outcomes of allo-HCT in this patient population are comparable to those in their counterparts without HIV. The risk of infections, GVHD, mortality and other complications are similar to patients without HIV infection. Review of this data also suggests that all patients with HIV with hematologic malignancies be started on ART as soon as possible if they are not already on it. This would help bring down the HIV viral load to undetectable levels and improve $CD4^+$ cell counts before HCT. Viral load and $CD4^+$ cell count must be closely monitored throughout the transplantation process, and involvement of an HIV expert is highly advisable. With the availability of small combination pills, patients should be able to maintain compliance with ART even if mild to moderate mucositis develops, and a parenteral form of ART like subcutaneous enfuvirtide may be helpful for

Table 5
Summary of Case Reports

Report	Patient	Hematologic Malignancy	Donor	Conditioning	GVHD Prophylaxis	GVHD Type	Post-HCT Effect on HIV	Outcome
Schlegel et al [15]	Male, 34 yr	CML	MSD	Bu/Cy	MTX/CSP	Severe chronic	Rebound ongoing ART (day +90)	CR on long-term follow-up
Soraa et al [16]	Female, 33 yr	AML	MSD	Bu/Cy	CSP	Acute grade II	HIV viremia undetectable with continuous HAART	CR at 39 mo
Shamansky et al [18]	Male, 47 yr	AML	MSD	Flu/Mel	MTX/CSP		NR	CR at 250-d follow-up
Tomonari et al [19]	Female, 23 yr	Ph$^+$ ALL	Double CBT	MAC	MTX/CSP	Acute grade I	HIV viremia with ART discontinuation, became undetectable on restarting ART	CR at 15-mo follow up
Avettand-Fenoel et al [20]	Male, 17 yr	AML	MUD	RIC	CSP/ATG	NR	Rebound, ongoing ART	Patient died of infection at 191 d post-HCT
Bryant et al [21]	Male, 34 yr	Peritoneal primary effusion-related lymphoma	MSD (previous auto-HCT)	RIC	Tacrolimus/ sirolimus/MTX	Acute grade I skin	Undetectable, on ART	CR2 at 31-mo follow up
Cummins et al [28]	Male, 55 yr	ALL	MUD	RIC with Flu/Mel	MTX/tacrolimus	Acute grade I GI	Rebound, ongoing ART	Continued CR

CML indicates chronic myelogenous leukemia; MSD, matched sibling donor; MTX, methotrexate; CSP, cyclosporine; NR, not reported; Ph$^+$, Philadelphia chromosome-positive; CBT, cord blood transplant; GI, gastrointestinal.

patients with severe mucositis. Protease inhibitors should be avoided because of interactions with conditioning chemotherapy and immunosuppressive agents used for GVHD prophylaxis. In 2017, Alvarnas et al [27] outlined the state-of-the-art management of hematologic malignancies in PLHIV and noted potential drug-drug interactions between ART and drugs used during HCT.

There remains the potential for infection of the allograft with HIV. Starting ART as soon as possible before HCT and achieving an undetectable viral load and continuing ART post-HCT with alterations to therapy when needed may help prevent this complication. In most of the cases in this series, when ART was stopped post-HCT, HIV viral load increased, although it promptly responded to reinstitution of ART.

The results of the first multi-institutional prospective trial, BMT CTN 0903, were reported by Ambinder et al in 2017 [14]. This trial reported the outcomes of 17 PLHIV with a median age of 47 years (range, 25 to 64 years) with hematologic malignancies who underwent allo-HCT between 2012 and 2015. Conditioning regimens included MAC in 8 patients and RIC in 9 patients. No TRM was reported in the first 100 days. The incidence of grade II-IV aGVHD was 41%. OS was 82% at 6 months and 57% at 12 months. HIV was detected in 2 of 3 patients who were mixed chimeras and in none of 2 who were 100% donor chimeras. This may reflect a graft-versus-HIV effect in these patients. In 2017, Cummins et al [28] described changes in the HIV reservoir in a patient with HIV who underwent allo-HCT for ALL by prospectively collecting peripheral blood mononuclear cells both before and after allo-HCT. They also studied the evolutionary development of HIV and phenotypic changes in the immune cells. At approximately 2 years post-HCT, after continuing undetectable HIV on multiple consecutive measurements, ART was stopped with the patient's consent and HIV was very closely monitored. They showed that allo-HCT led to a significant reduction in HIV reservoir size with a >9-month HIV replication-free interval off of ART. Rebound HIV was different from the pre-HCT HIV, suggesting a distinct phylogenetic origin.

HIV significantly affects the hematopoietic system, and ART has prolonged survival with excellent control but still is not curative. There has been a great deal of interest in immune therapies like HCT for curing this infection. The graft-versus-tumor/leukemia effect is appreciated in allo-HCT, providing cure of hematologic malignancies even in patients receiving RIC. Such a graft-versus-HIV reservoir effect has been hypothesized but not confirmed. The generation of a new immune system from donor stem cells with replacement of recipient immune cells infected with HIV seems attractive but has failed to eradicate HIV, likely secondary to infection of donor immune cells. There have been multiple reports of late relapse of HIV after allo-HCT after discontinuation of ART [29], which has been the case in this series as well.

The foregoing findings have led to efforts to use grafts resistant to HIV infection. CCR5 and/or CXCR4 are chemokine receptors required by HIV to enter the lymphocytes. The homozygous delta 32 mutation of CCR5 makes this receptor nonfunctional, and thus patients with this mutation are resistant to HIV infection. HCT from CCR5-delta 32 homozygous donors may theoretically lead to cure of HIV and eventual discontinuation of ART. In 2009, Hutter et al [23] reported the outcome of HLA-matched unrelated donor HCT for relapsed AML in a so-called “Berlin patient” with HIV using MAC [23]. The donor was homozygous for CCR5-delta 32 with inherent resistance to HIV infection. GVHD prophylaxis consisted of cyclosporine and ATG. HIV remained undetectable even at 20 months after discontinuation of ART. The patient developed grade I cutaneous aGVHD that

Table 6
Summary of Case Series

Study	Patients (Age, yr)	Hematologic Malignancy	Donor	Conditioning	GVHD Prophylaxis	Neutrophil Engraftment	GVHD Type	Post-HCT Effect on HIV	Infections	Outcome
Kang et al [17]	2 (31, 42)	t-AML (n = 1); primary refractory HL (n = 1)	MRD (n = 1); the patient with t-AML received genetically modified stem cells engineered to inhibit viral replication.	RIC (Flu/Cy)	CSP	NR	Grade II skin aGVHD (n = 2); cGVHD (n = 1)	HIV was undetectable in 1 patient with continued ART, and viral load increased in 1 patient after discontinuation of ART, but this patient responded to reinstitution.	CMV reactivation (n = 2); CNS toxoplasmosis (n = 1)	The patient with t-AML remained in CR with limited cGVHD. The patient with HL relapsed after treatment of GVHD and died of PD at 12 mo post-HCT.
Hamadani et al [22]	3 (39, 51, 55)	AML CR2, BL CR2, and plasmablastic lymphoma CR2	MRD (n = 1), MUD (n = 2)	RIC	Tacrolimus + MTX	NR	aGVHD skin (n = 1), limited cGVHD (n = 1), and extensive cGVHD (n = 1)	Two patients had an undetectable HIV viral load, at the time of HCT and the viral load of patient with plasmablastic lymphoma was 814 copies/mL. That patient developed rising HIV viral load at day +252 that responded to second-line ART.	CMV reactivation	All patients were alive at a median follow-up of 375 d, with no evidence of disease relapse.
Polizzotto et al [25]	3 (38, 41, 24)	MDS, AML, and T cell ALL	MRD, MUD	MAC	CSP	25 d (21-48 d)	None	HIV viral load was undetectable in all patients at the time of HCT. ART was discontinued but resumed months later owing to a rising HIV viral load.	BK polyomavirus cystitis, and *E coli* sepsis in 1 patient; multidrug-resistant pseudomonal sepsis	The patient with MDS died on day +730 in CR secondary to complications of renal failure. The patient with AML died of sepsis at day +78. The patient with T cell ALL died on day +105 secondary to relapse on day +101.
Serrano et al [11]	4 (37, 45, 44, 34)	DLBCL (n = 2), ALL and BL	MRD (n = 3), CBU and MMRD (n = 1)	MAC (n = 3) RIC (n = 1)	CSP (n = 1) CSP+MTX (n = 2) CSP + steroids (n = 1)	15 d (13 d-not reached)	Grade III aGVHD and extensive cGVHD (n = 1), grade II aGVHD and severe cGVHD (n = 1)	Undetectable on ART	Pulmonary aspergillosis (n=1)	The patient with pulmonary aspergillosis died of acute respiratory failure at day +6.
									CMV reactivation, pneumococcal pneumonia, multi-drug resistant Acinetobacter baumannii (n=1) BK polyoma virus cystitis and *E coli* sepsis (n = 1)	The second patient died after 36 mo in CR with severe GVHD and infection. The third patient died after 40 mo in CR with sepsis and multiorgan failure. The fourth patient had no evidence of GVHD and was alive in CR at 9-mo follow-up.
Johnston et al (prospective) [40]	8 (39, 33, 53, 43, 43, 39, 39, 54)	AML (n = 3), DLBCL (n = 1), MM (n = 1), CML (n = 1), HL (n = 1), BL (n = 1)	MRD (n = 1), MUD (n = 3), MMUD (n = 3), haploidentical (n = 1)	RIC (n = 6), MAC (n = 2)	CSP+MMF (n = 4), CSP +MTX (n = 2), PTCy+CSP (n = 1)	16 d (median)	Grade II-III aGVHD (n = 7)	All patients had an undetectable HIV viral load at HCT. NR after HCT.	CMV reactivation, RSV URI, rhizopus pneumonia, influenza pneumonitis, disseminated fusarium, adenovirus viremia, aspergillus pneumonia, *Clostridium difficile* colitis, and norovirus enteritis	Six patients died of relapse, and 1 patient died of idiopathic pulmonary syndrome.
Mulanovich et al [26]	5 (57, 51, 38, 55, 62)	AML (n = 2), MDS (n = 1), BL (n = 1), LGL leukemia (n = 1)	MRD (n = 2), MUD (n = 3)	RIC (n = 2), MAC (n = 3)	ATG (n = 2), NR (n = 3)	17 d (13-19 d)	aGVHD (n = 2); cGVHD (n = 1)	Undetectable on ART. One patient's viral load increased to 138 but then became undetectable on ART.	CMV reactivation (n = 4), acute cholecystitis (n = 1); rectal herpes (n = 1)	No TRM was reported within the first 100 days post-HCT. Patients with AML and MDS died of disease relapse. Two patients were alive in CR at long-term follow-up.

t-AML indicates therapy-related acute myelogenous leukemia; BL, Burkitt lymphoma; LGL, large granular lymphocytic leukemia; HL, Hodgkin lymphoma; MM, multiple myeloma; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MMF, mycophenolate mofetil; PTCy, post-transplantation cyclophosphamide; RSV, respiratory syncytial virus; URI, upper respiratory infection; PD, progressive disease.

responded to adjustment of the cyclosporine dose. The patient relapsed at 332 days post-HCT and underwent reinduction and a second HCT from the same donor. The patient remained in CR at a 20-month follow-up after second HCT.

CBU registries have undergone testing to identify units with CCR5-delta 32 homozygous mutated units that have been used for HCT in patients with HIV. In 2018, Hsu et al [30] reported an HIV-positive patient with AML who underwent CCR5-delta 32 homozygous 5/8 HLA- matched CBU and related haploidentical peripheral blood stem cell allo-HCT with Flu/Mel/TBI conditioning and GVHD prophylaxis with ATG, mycophenolate mofetil, and tacrolimus [30]. The post-HCT course was complicated by CMV reactivation, but HIV remained undetectable on continuing ART. Chimerism studies favoring haploidentical donor cells earlier in the post-HCT course converted to 100% CBU later in the course. The patient continued to be in CR at an 11-month follow-up. Long-term viral studies are awaited for this case. There have been few other reports of dual CBU and haplo-HCT. Which graft would eventually take over remains an open question, however, that can be answered only after HCT. A dual CCR5-delta 32 homozygous CBU/haploidentical transplantation was performed in a patient with HIV and DLBCL [31]. Early neutrophil engraftment was of haploidentical donor origin, and CBU failed to engraft. The patient received a second CCR5-delta 32 homozygous CBU infusion on day +52 and achieved 100% confined blood cell chimerism on day +73. Engrafted lymphocytes were resistant to HIV infection. The patient died of progressive lymphoma at 3 months post-HCT. Another such transplantation was performed in a PLHIV with high-risk myelodysplastic syndrome, who achieved CBU engraftment but died of pneumonia and MDS relapse 2 months post-HCT [32].

The prevalence of homozygous mutation of CCR5-delta 32 occurs in only approximately 1% of Caucasians of northern European descent. Its prevalence in other population groups is much lower, leading to a very low likelihood that a potential HLA-matched unrelated donor is homozygous for this mutation. Heterozygous mutation of CCR5-delta 32 does not confer resistance to HIV infection. If a graft could be engineered to be negative for CCR5, this benefit of HIV resistance could be available to a larger population of patients. Genetic alteration of the graft to make it resistant to HIV infection has been attempted, as reported by Kang et al [17].

In some patients who received transplants from donors with homozygous mutation of CCR5-delta 32 had increase in viral load following cessation of ART, suggesting that other factors may be involved. One such mechanism is selection of CXCR4 for cellular entry [33,34]. Thus, other approaches that render grafts resistant to HIV infection with the aid of gene therapy are underway. These include stem cells expressing anti-HIV small RNAs, such as RNA against HIV tat/rev, anti-CCR5 ribozyme (ClinicalTrials.gov identifiers NCT00569985 and NCT01961063), and coexpression of short hairpin RNA against CCR5 and HIV entry inhibitor peptide C46 (NCT01734850). Also of interest, because of the extremely low of CCR5-delta 32 homozygous mutation, is selecting heterozygous CCR5-delta 32 mutated stem cells that are relatively more prevalent. Inducing a mutation of 1 allele may be a relatively quick approach compared with genetically engineering CCR5 wild-type cells to induce mutation of 2 alleles [34].

Another option to consider is the generation of HIV-specific CD8 T cells and a graft-versus-HIV reservoir effect. New HIV-specific CD8 T cells can be generated from an HIV-naive donor early after HCT [13]. This response can be generated even in patients with an undetectable HIV viral load, suggesting that HIV viremia might not be required for this T cell response, because lymphatic tissues express a low volume of HIV antigens that can cause priming of these T cells. This is suggested by several reports in which after achievement of full donor chimerism, recipient lymphocytes latently infected with HIV were reduced over time. Factors implicated in this response require further study to generate such responses in the majority of patients. The eradication of latent HIV reservoir cells after virus reactivation is dependent on stimulation of HIV-1- specific cytotoxic T cells [35]. In 2016, Patel et al [36] reported that HIV-specific T cells can be generated and expanded from HIV-naïve donors in vitro. A fraction of these T cells expressed a phenotype of memory cells, suggesting the potential for long-term persistence of HIV-specific T cells after infusion, providing recipients with long-term immunity. These T cells become activated only after exposure to HIV antigens. The generation of such naïve donor-derived HIV-specific T cells with expansion and infusion after allo-HCT could provide long-term control and even cure of HIV infection along with the cure of primary hematologic malignancies. In 2018, Patel et al [37] reported that such multi-HIV antigen-specific T cells could be generated from HIV-naïve donors as well as from CBUs [37]. This is important, because the donor may serve as a source for both stem cells and HIV-specific T cells, and the ability to generate HIV-specific T cells from cord blood and haploidentical donors could make this strategy available to potentially all PLHIV undergoing allo-HCT for hematologic malignancies.

The effect of the dendritic cell vaccine pulsed with inactivated host HIV on the HIV reservoir while holding ART has been studied. This vaccination produced HIV-1-specific T cell responses that caused a delay in restoration of the viral reservoir after discontinuation of ART in study subjects [38]. Scholler et al [39] reported a combined analysis of the long-term safety and efficacy of chimeric antigen receptor (CAR) T cells designed for HIV from 3 clinical studies. The patients showed long-term persistence of these CAR T cells, and none developed any hematologic disorders [39]. This therapy may have a role in eradication of the HIV reservoir either pre- or post-HCT and needs to be studied in that setting.

CONCLUSION

ART has improved outcomes in patients with HIV, with marked reductions in morbidity and mortality leading to an increased prevalence of PLHIV at risk for both lymphoid and myeloid hematologic malignancies. Transplantation outcomes have generally improved with progress in supportive care, donor availability, and refined conditioning regimens, as analyzed in this review. PLHIV, just like their uninfected counterparts, should be offered allo-HCT, a potentially curative therapy, whenever indicated for hematologic malignancies. Patients not already receiving ART should be started on it immediately after diagnosis and continued throughout HCT with close monitoring of HIV viral load, $CD4^+$ T cell count, adverse effects, and drug-drug interactions. The involvement of HIV experts is strongly recommended. If a transplantation center does not feel comfortable treating such patients, prompt referral for consultation at a center where experts are available is recommended. A donor with a homozygous CCR5-delta 32 mutation is preferred whenever available, and if the donor is being searched for in the unrelated donor registry, then it is preferable to contact the immunologist at the registry specifically to request a custom search for a homozygous CCR5 donor. Based on this principle, some innovative trials are already underway (ClinicalTrials.gov identifiers NCT02140944 and NCT03164135). In addition, progress in gene therapy with

modification of the graft for resistance to HIV infection might prove curative not only for the hematologic malignancy, but also for HIV in this growing population.

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