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TRANSPLANT AND ONCOLOGY (M ISON, SECTION EDITOR)

HIV and Stem Cell Transplantation

Ignacio A. Echenique · George E. Nelson · Valentina Stosor · Christine M. Durand

Abstract In human immunodeficiency virus (HIV)-infected persons, the incidence of hematologic malignancies, including leukemia and lymphoma, is increased despite the use of successful antiretroviral therapy. Hematopoietic stem cell transplantation (SCT) is emerging as a safe and effective therapy for HIV-infected persons with hematologic malignancies. Management of these patients is complicated by drug–drug interactions involving antiretroviral therapy (ART) that may impact conditioning agent efficacy and metabolism of immunosuppressive medications and potentiate drug toxicities. As such, optimal strategies for ART remain controversial. We discuss recent advances, controversies, and future directions related to SCT in HIV-infected persons, including the investigation of allogeneic SCT as a strategy for HIV cure.

Keywords AIDS · Allogeneic stem cell transplantation · Antiretroviral therapy · Autologous stem cell transplantation · Bone marrow transplantation · GVHD · HIV · HIV cure · HIV eradication · HIV reservoir · Hodgkin lymphoma · Non-Hodgkin lymphoma · Stem cell transplantation

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Ignacio A. Echenique and George E. Nelson these authors contributed equally to the work

I. A. Echenique · V. Stosor
Division of Infectious Diseases, Department of Medicine, Northwestern University Feinberg School of Medicine, 645 N. Michigan Ave, Suite 900, Chicago, IL 60611, USA

I. A. Echenique
e-mail: Ignacio.echenique@northwestern.edu

V. Stosor
e-mail: v-stosor@northwestern.edu

V. Stosor
Division of Organ Transplantation, Department of Surgery, Northwestern University Feinberg School of Medicine, 645 N. Michigan Ave, Suite 900, Chicago, IL 60611, USA

G. E. Nelson · C. M. Durand
Division of Infectious Diseases, Department of Medicine, Johns Hopkins School of Medicine, 1830 E. Monument Street, Suite 450B, Baltimore, MD 21287, USA

G. E. Nelson
e-mail: george.nelson@jhmi.edu

C. M. Durand (✉)
Division of Infectious Diseases, Johns Hopkins School of Medicine, Miller Research Building, Room 869, 733 North Broadway Street, Baltimore, MD 21204, USA
e-mail: christinedurand@jhmi.edu

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ADM	AIDS-defining malignancies
alloSCT	Allogeneic stem cell transplantation
autoSCT	Autologous stem cell transplantation
CNI	Calcineurin inhibitor
CFAR	Center for AIDS Research
CCR5	Chemokine receptor 5
ART	Combination antiretroviral therapy
CBT	Cord blood transplant
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CyA	Cyclosporine
CYP450	Cytochrome p450
HL	Hodgkin lymphoma
INSTI	Integrase Strand Transfer inhibitor
KS	Kaposi sarcoma
mTOR	Mammalian target of rapamycin
NADM	Non-AIDS-defining malignancies
NHL	Non-Hodgkin lymphoma
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside or nucleotide analogue reverse transcriptase inhibitor

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PI	Protease inhibitor
SIR	Standardized incidence ratio
SCT	Stem cell transplantation
SEER	Surveillance, Epidemiology, and End Results Program registry
TAC	Tacrolimus
UDP-1A	Uridine diphosphate glucuronyltransferase-1A

Introduction

Human immunodeficiency virus (HIV)-infected individuals are at increased risk for a range of hematologic cancers for which stem cell transplantation (SCT) is considered standard therapy. Early in the AIDS epidemic, HIV-infected individuals were not offered this aggressive therapy, due to increased mortality. However, with the improvements afforded by effective combination antiretroviral therapy (ART) and other advances in cancer care, many centers now offer HIV-infected persons SCT for the treatment of hematologic malignancies, including acute leukemia, primary-refractory and relapsed non-Hodgkin lymphoma (NHL), and relapsed Hodgkin lymphoma (HL). In this unique confluence of circumstances, the potential of SCT is also being examined as a mechanism for HIV cure.

Overall Rates of Hematologic Malignancies and Outcomes

The increased risk for malignancies was identified as a feature of the early AIDS epidemic, and several malignancies are recognized as AIDS-defining, including Kaposi sarcoma (KS) and certain forms of NHL, including diffuse large B cell lymphoma, Burkitt lymphoma, and primary central nervous system lymphoma [1]. An increased rate of other, non-AIDS-defining malignancies (NADMs) is also recognized, including HL and leukemia [2].

The incidence of AIDS-defining malignancies (ADMs) and NADMs has undergone a variety of changes in the ART era. Rates of ADMs, including NHL, have largely fallen [2–6], although within NHL there is an increasing proportion of Burkitt lymphomas [6, 7]. Additionally, the reported rates of HL, an NADM, have remained constant [4, 8–11] or increased [2, 3, 12–14]. Regardless, the risk for NHL and HL remains greater than for the general population [3, 15, 16]. For instance, the standardized incidence ratio of NHL in HIV-infected individuals from 1996 to 2002 was 22.6 [95% CI 20.8–24.6], as compared with that of the general population enrolled in the Surveillance, Epidemiology, and End Results Program registry [3].

In the Center for AIDS Research Network of Integrated Clinical Systems cohort, among incident cancer cases diagnosed in ART-treated patients from 1996 to 2009, NHL comprised 18%, primary central nervous system NHL 3%, and HL 5% [17]. While hematologic malignancies did not represent the majority of incident cancers (KS, 29%; lung, 9%; and anal, 8%), they remain an area of concern. In this cohort, leukemia occurred in a small minority of patients, but an increased risk has been described in other studies [18, 19]. Overall, although the cumulative risk of death has fallen in the ART era, the consequences of malignancy are profound: cancer-related mortality is a leading cause of death in HIV-infected persons [20, 21]. Data suggest that it is not merely virologic control but the duration of viremia, the degree of immune reconstitution, and age that influence the risk of cancer [22, 23]. The benefits of immune restoration remain incompletely characterized but are known to be associated with reduced long-term mortality in general and decreased risk for malignancy specifically, particularly when the CD4 cell count is >500cells/mm^3 [23–25]. Since there is an enhanced and more durable CD4 cell count recovery when ART is initiated earlier, early HIV treatment may mitigate the downstream effects of chronic inflammation [26, 27].

Hematopoietic Stem Cell Transplantation as a Therapy for Hematologic Malignancies in HIV-Infected Persons

Before the introduction of ART, chemotherapy for HIV-related malignancies was associated with considerable toxicity and worse outcomes than in the HIV-uninfected population, leading to the use of reduced-intensity regimens [28]. In the ART era, higher rates of opportunistic infections and other complications have not been observed. Therefore, it has become well established that HIV-infected individuals can and should receive standard chemotherapy [29–31].

Autologous SCT (autoSCT) has been shown to be well tolerated and efficacious in the treatment of HL and NHL. Prospective trials have reported overall survival that ranges from 60% to 85%, with SCT-related mortality ranging from 0% to 5% (Table 1) [32–35]. Case–control trials have not demonstrated a statistically significant difference in overall survival or infectious complications between HIV-infected and uninfected individuals [36, 37].

The experience with allogeneic SCT (alloSCT) is not as robust as with autoSCT and is limited to case reports and small series. In general, the post-ART era has seen substantial improvement in patient survival after alloSCT for hematologic disorders [38•, 39, 40]. Prospective clinical trials are underway, but there are no published results to date.

Pharmacologic Considerations

The treatment of HIV-infected individuals undergoing SCT is complicated by the interplay of ART, conditioning chemotherapy, graft-versus-host disease prevention and treatment

Table 1 Survival and complications in trials of HIV-infected persons with Hodgkin lymphoma and non-Hodgkin lymphoma undergoing autologous stem cell transplantation (autoSCT)

	Year	Number of HIV-Infected Persons	Overall Survival (%), Median Follow-up	SCT-Related Mortality (%)	Infection-Related Mortality (%)
AutoSCT prospective trials					
[33]	2003	16	60%, 2–4 months	0%	0%
[32]	2005	20	85%, 32 months	5%	0%
[34]	2005	11	64%, 28 months	0%	9%
[35]	2008	20	74%, 23 weeks	5%	0%
AutoSCT case–control					
[36]	2009	53	58.5%, 30 months	0%	7.6%
[37]	2010	29	75%, 24 months	0%	3.4%
[84]	2010	24	NR	NR	8.3%
AutoSCT retrospective					
[108]	2000	2	20, 28 months	–	–
[56]	2004	14	36%, 12 months	0%	0%
[58]	2009	68	61%, 36 months	NR	NR
[109]	2011	1	16 months	–	–

agents, and antiinfective agents. There is tremendous heterogeneity among regimens, as well as known and theoretical drug–drug interactions. Given the lack of data in HIV-infected persons that inform these interactions and resulting complications, optimal protocols are unclear. Therefore, approaches must be individualized. To optimize outcomes, we favor a multidisciplinary management approach, combining expertise in infectious diseases, hematology-oncology, and pharmacology.

ART Drug–Drug Interactions with Chemotherapy

There is no single recommended or preferred ART regimen in patients receiving chemotherapy or immunosuppression. However, when feasible and on an individual basis, it is prudent to modify the ART regimen to avoid drug–drug interactions and toxicities. Additional factors to take into account when choosing or modifying ART include antiretroviral resistance profiles, CCR5/CXCR4 co-receptor status or tropism, concurrent illnesses, and comorbidities.

Approved antiretroviral drugs include 20 medications from six different classes: nucleoside or nucleotide analogue reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and the entry inhibitors including the fusion inhibitor enfuvirtide and the CCR5 antagonist maraviroc. The drug–drug interactions of PIs and NNRTIs with chemotherapeutic agents are among the best characterized yet still incompletely understood. Largely, this interaction occurs through the cytochrome P450 (CYP) enzyme system, particularly with CYP3A4. Bioavailability may also be influenced by the intestinal P-glycoprotein efflux pump, whose function is influenced both by host polymorphisms and by CYP3A4 itself [41].

There are concerns regarding the interaction between ART and the SCT conditioning regimens. For example, cyclophosphamide is metabolized by the CYP450 system, with increased exposure with concomitant PI-based inhibition and, potentially, greater toxicity. Bower et al. compared PI-containing and PI-sparing ART in NHL patients treated with cyclophosphamide, doxorubicin, and etoposide. Among the 11 PI-treated patients, more frequent infections requiring hospitalization were noted (implying intensified effects of chemotherapy), but there were no differences in complete response rates, disease-free survival, or overall survival [42]. Wong et al. examined PI-containing and -sparing regimens in patients who received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy. There were no differences in adverse events, and both groups had similar outcomes [43]. The potential for enhanced toxicity is of concern in PI-treated patients, although this complication has not been clearly demonstrated in limited data. In this context, experts recommend avoiding PIs during conditioning chemotherapy if an alternative antiretroviral drug can be substituted. A summary of relevant interactions is presented in Table 2.

In transplantation, the calcineurin inhibitors, cyclosporine (CyA) and tacrolimus (TAC), are commonly employed in the prevention and treatment of graft-versus-host disease. Dose and dosing intervals are established in individual patients with therapeutic drug monitoring. Due to inhibition of CYP34A, PIs, especially ritonavir, lead to increased serum concentrations of CyA and TAC. To avoid supratherapeutic calcineurin-inhibitor exposure and associated toxicities, reductions of dose and dosing intervals are necessary. In practice, this

Table 2 Antiretroviral therapy considerations during stem cell transplantation

	CYP450 Interaction	Oncologic Management Considerations
NRTIs		
Abacavir	Not anticipated	–
Didanosine	Not anticipated	–
Emtricitabine	Not anticipated	–
Lamivudine	Not anticipated	–
Stavudine	Not anticipated	–
Tenofovir	Not anticipated	–
Zidovudine	Not anticipated	–
NNRTIs	CYP450 inducer	May decrease CNI levels
Efavirenz	CYP450 inducer	May decrease CNI levels
Nevirapine	CYP450 inducer	May decrease CNI levels
Etravirine	CYP450 inducer	May decrease CNI levels
Rilpivirine	Substrate of CYP3A4	Minimal known effect
Ritonavir-boosted PIs (classwide effect)	CYP450 inhibitor	May increase CNI levels
Integrase strand-transferase inhibitors		
Raltegravir	UDP-1A	Unknown
Cobicistat/Elvitegravir	CYP450 inhibitor (cobicistat)	May increase CNI levels
Dolutegravir	Unknown/not anticipated	–
CCR5 antagonist		
Maraviroc	CYP3A4 substrate	Unknown
Fusion inhibitor		
Enfuvirtide	Unknown/not anticipated	–
Immunosuppressants		
Maintenance		
mTOR-inhibitors	CYP3A4 and P-glycoprotein substrates	CYP3A4 inhibitors may diminish therapeutic drug levels
Calcineurin-inhibitors	CYP3A4	CYP3A4 inhibitors may diminish therapeutic drug levels
Antiinfectives		
Azoles	May inhibit CYP3A4	May increase CNI levels
Fluoroquinolones	Not anticipated	–
Sulfamethoxazole/Trimethoprim	Not anticipated	–
Valganciclovir	Not anticipated	–

Note. mTOR, mammalian target of rapamycin; CNI, calcineurin inhibitor; NRTI, nucleoside or nucleotide analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; CCR5, chemokine receptor 5

interaction has been best examined in HIV-infected solid organ transplant recipients [44, 45]. Although levels are altered, titration to goal is not insurmountable but must be individualized. Some have suggested that the altered pharmacokinetic curve in patients receiving both PIs and TAC may actually necessitate a rise in the goal trough level of TAC to maintain an adequate area under the curve [46].

Of the NNRTIs, particularly efavirenz and nevirapine may induce the CYP450 system and require calcineurin-inhibitor adjustment [47]. Rilpivirine does not appear to induce the CYP450 system, presenting a favorable alternative. Due to these complexities, collaboration with transplant pharmacology colleagues is critical for optimizing calcineurin inhibitor use in the setting of concomitant PI or NNRTI use. Some approaches include a pretransplantation dose finding to assess adequate exposure posttransplant.

Among the INSTIs, raltegravir is an attractive option given that it is metabolized largely by uridine diphosphate glucuronyltransferase-1A (UDP-1A). Using the solid organ transplant experience as an analogue, drug interactions have been minimal [48, 49]. Experience with dolutegravir is limited, but, like raltegravir, it is largely metabolized by UDP-1A and does not induce or inhibit CYP450 isoenzymes. Elvitegravir is co-administered with cobicistat, a potent CYP3A4 inhibitor; therefore, its use should be avoided if possible.

Maraviroc is the first-in-class CCR5 antagonist for the treatment of HIV infection and is of particular interest in the

setting of SCT. Maraviroc inhibits the most common strains of HIV that use the cellular chemokine receptor CCR5 to infect cells. It is a small molecule inhibitor that prevents the binding of the HIV envelope protein gp 120 to CCR5 [50] In addition, blockade of this receptor has been shown to impair lymphocyte chemotaxis, and in HIV-uninfected individuals receiving SCT, it has been shown to reduce the incidence of severe graft-versus-host disease [51].

Finally, one must be mindful of the overlapping profiles of concurrent medications used in the treatment of HIV and SCT. For instance, sulfamethoxazole-trimethoprim may worsen myelosuppression. Dose adjustment of medications amid altered renal function may also be necessary, particularly with tenofovir.

Treatment Interruptions: Avoid Where Possible

Planned treatment interruptions were pursued in the early ART era in an attempt to balance drug toxicities with immunologic recovery. Subsequent studies demonstrated that this strategy had disadvantages, including higher HIV viral loads and lower CD4 counts, increased morbidity, mortality, and perhaps antiviral resistance [52–54]. ART interruption can also be problematic when components of the regimen have different half-lives, since this can result in periods of functional monotherapy, during which antiretroviral resistance can develop [55]. The minimum safe time for a treatment interruption, if any, has not been established [55]. Adverse effects of ART interruptions have been reported in as little as 4 weeks to 3 months. Nonetheless, there are practical considerations that may preclude effective oral medication administration, as well as chemotherapy-induced mucositis, nausea, and vomiting. These absorption and administration issues may be mitigated with the arrival of injectable and long-acting ART.

In autoSCT, varying ART continuation strategies have been utilized. Some studies have required that ART be maintained [32, 33, 56], whereas others have described interruptions only when administration could not be tolerated [57, 58]. Quantification of the treatment interruptions and their durations is limited; one study reported that 22.5% of enrollees had some form of interruption [58]. Subsequent virologic failure is not described but remains a theoretical concern.

Reports of alloSCT in HIV-infected patients note heterogeneous ART strategies, including planned and unplanned interruptions [40, 59–64]. Uniformly, those who had ART interrupted developed a rebound viremia and insome instances, an acute febrile illness occurred akin to primary HIV infection [65]. Nonetheless, all patients became virologically suppressed when ART was reinitiated.

Thus, although there are no randomized trials to this effect, we feel the weight of evidence strongly favors ART continuation without interruption. First, there has been a significant improvement in overall survival with the advent of ART for patients with hematologic malignancies treated with myeloablative chemotherapy as well as alloSCT. In addition, a recent study demonstrated that patients with lymphoma who were started on ART early and achieved virologic suppression had improved outcomes [66]. Finally, maintaining ART during alloHSCT may prevent infection of naïve donor cells and have downstream benefits insofar as a reduced viral reservoir and the increasingly evident benefits therein [27, 59, 67].

Stem Cell Transplantation as a Strategy for HIV Cure

SCT has been investigated as a strategy to treat HIV infection since the beginning of the epidemic. Even before the HIV virus was discovered, SCT was used as an attempt to reverse the profound immunodeficiency of AIDS. In 1983, Hassett et al. reported experiences using alloSCT from HLA-matched donors in 2 patients with Kaposi sarcoma and recurrent opportunistic infections [68]. No cytotoxic conditioning regimen was thought to be necessary, due to the patients' profound immunodeficiencies. No stable engraftment of donor cells or improvement in immunologic status was observed. Further attempts of SCT alone as a strategy for AIDS treatment were unsuccessful [69].

In 1987, zidovudine, which had originally been developed for cancer treatment, was repurposed for the treatment of HIV with approval for use in the United States [70]. By 1989, zidovudine in concert with alloSCT was used in an HIV-infected individual with refractory lymphoma [71]. The patient died due to tumor relapse, but postmortem analysis showed no evidence of HIV by culture or PCR, forming the basis upon which the authors suggested that HIV-infected recipient cells were possibly eradicated. This strategy was further investigated in a partially randomized placebo controlled trial where HIV-infected persons without cancer who had identical twins were randomized to SCT plus either zidovudine or placebo [72]. No differences in virologic measures were noted, and there were only transient immunologic benefits. Similar protocols fared no better [73–76]. Later advances in the understanding of HIV allowed reevaluation of SCT as a curative strategy.

Barriers to HIV Cure

There is great interest in finding a cure for HIV. Various types of cure have been proposed, including "sterilizing cure," in which all traces of the virus are eradicated from an individual, and "functional cure," in which an individual can remain without clinical disease, or in remission, without requiring antiretroviral therapy. The most completely described barrier to HIV cure in individuals on effective ART is latent

replication-competent HIV, which persists in long-lived resting memory CD4+ T cells [77–79].

To achieve HIV cure, effective SCT must fulfill two criteria: eradication of replication-competent HIV from reservoirs and prevention of viral transmission to donor cells. In addition to the resting memory CD4+ T cell population, there is conflicting evidence regarding whether HIV persists long term in other cells, such as hematopoietic progenitor cells and tissue-derived macrophages, including microglial cells in the brain [80–83]. All of these proposed reservoirs are in cells of hematopoietic origin, supporting the concept of SCT as a strategy to eradicate HIV infection. In the process of SCT, hematopoietic-derived cells are destroyed by a combination of cytotoxic chemotherapy and graft-versus-host effects, with the intent of replacement by donor cells. Early trials attempted to leverage this graft-versus-hematopoietic effect to eradicate HIV reservoirs in the recipient, but prevention of HIV infection of donor cells remained elusive [71–76]. AutoSCT has been investigated as a strategy of cure amid continuing ART but has been unsuccessful in this regard, suggesting that cytotoxic therapy alone does not significantly reduce HIV reservoir size [57, 84] The discovery that HIV uses cellular co-receptors CCR5 and CXCR4 for entry into cells revealed that patients with a homozygous 32-base pair deletion in the CCR5 gene (CCR5Δ32) lacked expression of CCR5 and displayed high-level resistance to the most common variants of HIV [85–90]. Thus, it was surmised that matched CCR5Δ32 donors would have a virologic advantage. This strategy was proposed in the early 2000s but required the confluence of two rare circumstances: an HIV-infected person with a malignancy requiring alloSCT and the identification of a human leukocyte antigen (HLA) matched donor who was homozygous for CCR5Δ32 [91].

The "Berlin" Patient

Hütter et al. reported the only confirmed case of HIV cure with allogeneic SCT from a CCR5Δ32 donor in 2009 [67]. The so-called Berlin patient had well-controlled HIV infection when he was diagnosed with acute myelogenous leukemia requiring an SCT. The Seattle, Washington native was living in Berlin, Germany at the time he received an SCT from a donor specifically selected as homozygous for CCR5Δ32. ART was discontinued at the time of transplant, and in interim follow-up over 6 years, there was no evidence of replication competent proviral HIV DNA in blood or tissues [92]. The outcome in this remarkable case has been attributed to a combination of cytotoxic therapy, the graft-versus-hematopoietic effect, and protection of the new donor cells by CCR5Δ32.

To date, the case of the Berlin patient has not been replicated, due to challenges in the identification of appropriate donors [93–95]. Cord blood transplants from CCR5Δ32 have been suggested as a possible solution, due to less stringent HLA matching requirements [96]. There have been other efforts utilizing cord blood transplant (CBT) for HIV cure, but enthusiasm has been tempered by the associated increased risk of infections during engraftment [97, 98]. The greatest applicability insofar as risk and benefit may be in pediatric patients. In April 2013 at the University of Minnesota, a child with HIV/AIDS simultaneously afflicted with acute lymphocytic leukemia underwent the first CBT in the United States with a CCR5Δ32 matched donor with the intent of achieving an HIV cure. The patient unfortunately died of complications due to graft-versus-host disease before it could be established whether HIV cure was achieved [99]. An AIDS Clinical Trials Group trial remains underway in the prospective evaluation of this strategy in pediatric patients [100].

Seeking wider applicability and greater scalability, small studies have investigated autoSCT coupled with gene therapy to selectively delete CCR5 receptors, creating a functional CCR5Δ32 homozygous immune system [62, 101–105].

The "Boston Patients"

Henrich et al. described the disappearance of HIV reservoirs in 2 individuals following reduced-intensity conditioning alloSCT [106]. Unlike the Berlin patient, these individuals, known as the Boston patients, remained on ART throughout the alloSCT and had CCR5 wild type (HIV-susceptible) donors. Extensive testing of blood and tissues in these individuals revealed no evidence of HIV, and donor cell replacement appeared complete (<0.001% of residual host peripheral blood mononuclear cells). Under research protocol, the patients consented to interruption of ART. Unfortunately, the patients experienced viral rebound at 12 weeks and 32 weeks, respectively, with symptoms consistent with an acute retroviral syndrome. Single genome sequencing of HIV-1 envelope confirmed that the rebound virus was highly similar (>96% nucleotide identify) to pre-SCT virus, excluding the possibility the patients were newly infected [106, 107]. These findings suggest that alloSCT in combination with ART can reduce the size of the HIV reservoir substantially but may not eradicate infected host cells completely and/or is insufficient to prevent infection of donor cells.

Conclusions

Incidences of malignancies including HL and NHL are changing amid successful antiretroviral therapy and an aging HIV-infected population. Hematopoietic SCT has been demonstrated to be a safe and effective cancer treatment in HIV-infected persons. There are pharmacologic concerns, both known and theoretical, that complicate management, including drug–drug interactions that may impact induction efficacy, altered levels

of immunosuppressants, and potentially compounded toxicities. As such, optimal strategies for ART during induction are controversial. Among modalities, SCT is of particular interest given the unique confluence of circumstances that allows evaluation for HIV cure strategies.

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Compliance with Ethics Guidelines

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