Haematopoietic stem cell transplantation in an HIV endemic area: time to consider HIV exposed or infected donors

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Word count: 4124

Summary:

South Africa (SA) has more than 8 million people living with human immunodeficiency virus (HIV) (PLWH). In contrast, the number of patients receiving a haematopoietic stem cell (HSC) transplant (HSCT) in SA is far below the target number. Donor numbers are insufficient to meet the demand. Success has been achieved with HSCT in PLWH as recipients and in solid organ transplantation (SOT); in the case of the latter, this has been achieved in settings in which both donors and recipients have been HIV-infected. This manuscript explores the possible inclusion of PLWH as well as umbilical cord blood (UCB) from HIV exposed uninfected (HEU) infants as donor sources for HSCT. Beyond the risk of contraction of HIV, additional complications such as delayed or inadequate immune reconstitution and an increased risk of haematological abnormalities and malignancies, must be considered. Interactions between antiretroviral drugs and drugs used in the conditioning regimen as well as the need to maintain virological suppression when gastrointestinal absorption deteriorates, are additional complicating factors. The process also requires more stringent ethical processes to be in place to minimise physical and emotional harm. In an HIV endemic country however, HIV infected or exposed donor sources must be considered as part of a multi-disciplinary collaborative effort to provide more patients with the opportunity to receive a life-saving HSCT.

Introduction

Access to haematopoietic stem cell transplantation (HSCT) in South Africa (SA) is very limited. The lack of human leukocyte antigen (HLA) matched donors is a major factor and has limited the development of transplantation skills due to the paucity of transplants performed. Local donor registries are trying to improve donor representivity to be in keeping with a population that consists of >90% African, Mixed-race and Indian/Asian individuals(1), but individuals of European descent are still overrepresented in comparison.(2) Genetic diversity in the African ethno-linguistic groups is particularly significant and as a result the chances of finding a suitable donor for HSCT is <20%(3) much less than individuals of European descent where it is >80%. The 2019 European Society for Blood and Marrow Transplantation (EBMT) survey on transplant activity in SA in 2019 (unpublished) reports 357 HSCTs performed, inclusive of autologous and allogeneic transplants (allo-HSCT), at a rate of approximately 6/million per annum in the 60 million SA inhabitants.(1) This is a far cry from the 15-30/million/annum provided in high-income countries.(4) The deficit in transplantation access based on these figures is thus approximately 1443 patients per annum, based on an expected rate of 30/million per annum. Beyond the limitations related to infrastructure and human resources, SA has an additional and unique factor to consider: endemic infection with human immunodeficiency virus (HIV). Our country has 8,2 million people living with HIV (PLWH) making up an estimated 13,7% of the total population.(5) Home to the world's largest antiretroviral (ARV) roll-out programme, 66,9% of PLWH in SA are on ARVs.(6) HIV related deaths now constitute 12,2% of total annual deaths in SA, a marked reduction from the peak of 39,7% in 2006.(5) In the context of HSCT, the high HIV burden adds a further level of complexity. Donors LWH in the context of solid organ transplantation (SOT) has been extensively explored, but HSCT has not featured in this debate. As we move towards increasing our donor base to make HSCT more accessible, the questions and fears around transplantation from a donor LWH to an HIV-negative recipient (D+/R-) or a recipient LWH (D+/R+) will have to be considered by South African clinical haematologists/oncologists when managing these patients.

The purpose of this paper is to review what is known about HIV in the context of SOT and HSCT, the possible role of umbilical cord blood (UCB) from HIV exposed uninfected (HEU) infants as a stem cell (SC) donor source, and the ethical considerations related to potential HIV-infected or exposed donors.

HIV in solid organ transplantation

SOT in recipients LWH has been shown to be acceptable, with outcomes comparable to HIV-negative recipients.(7) Initially, donors had to be HIV-negative but with the scarcity of organ donors and improved life expectancies of PLWH, the ethics of excluding PLWH as donors came under scrutiny.(8) Three-year patient and graft survival has been shown to be reduced in D-/R+ liver transplants compared to D-/R- transplants.(9) In another report, PLWH with a model for end stage liver disease (MELD) of 15 or above showed a survival benefit post liver transplant, while D-/R+ kidney transplant (R+) showed similar outcomes as their D-/R- counterparts.(7) Heart and lung transplant survival in R+ are reported to be similar to HIV negative patients, although rejection rates in heart transplant recipients are higher.(10)

D+/R+ SOT was first described by Muller et al(11) and subsequently described by others.(12) This practice, initiated by the HIV Organ Policy Equity (HOPE) Act and regulated by clinical research trials,(13) has been a positive step towards eliminating the fear, anxiety and stigma associated with HIV-infection. Reports show that D+/R+ liver transplant recipients have a higher rate of cancer and infections, and subsequently mortality rates compared to D-/R+ transplant recipients.(14) Graft survival was however not affected. In (D+/R+) kidney transplants, there were no differences in deaths or graft survival; however, higher rates of graft rejection were found compared to the D-/R+ cohort.(15)

The first D+/R- SOT described was after a partial liver transplant from a mother LWH to her HIV-negative child at Wits Donald Gordon Medical Centre (WDGMC) in SA.(16) In the WDGMC case, the treating team acknowledged the difficulty in confidently determining the HIV status of the child in question, as he had been on ARVs since the transplant.(16)

HIV in haematopoietic stem cell transplantation

The evaluation of a suitable donor for HSCT has to prioritise the safety of the donor for the process of SC collection, as well as ensuring the recipient is not exposed to any transmissible diseases.(17) HIV-1 and -2 are exclusion criteria as are a host of other communicable diseases.(17) Transfer of autoimmune diseases from recipient to donor has also been shown,(18,19) emphasising the importance of good general donor health.

PLWH who have undergone HSCT have no increased risk of mortality or graft-versus-host disease (GVHD) compared to HIV-negative recipients.(20,21) In the setting of allo-HSCT however, higher rates of infection, particularly cytomegalovirus (CMV) and non-tuberculous

mycobacteria, have been reported.(20) Small case series of allo-HSCT in PLWH have highlighted the following: ARVs should not be interrupted in the post HSCT period(22), haploidentical and UCB donors can be considered(21,22), and engraftment is not affected by HIV status.(21–23) One report describes immune reconstitution post HSCT in PLWH (R+) showing similar CD4+ T-cell recovery, but a significant increase in CD8+ T-cells from 9 months post HSCT, compared to HIV uninfected HSCT recipients.(24) Another study reports incomplete immune reconstitution years after HSCT.(25) The consensus is that PLWH should receive an HSCT if clinically indicated, provided they adhere to the normal recipient criteria.(26) Certainly, recent outcomes are far superior to initial efforts, and it is reasonable to suggest that experienced centres should guide the way forward. A group from Johns Hopkins has described the use of post-transplant cyclophosphamide (PtCy) for GVHD prophylaxis in their 9-patient cohort, paving the way for consideration of more donors.(22) These patients had high-risk haematological malignancies and enfuvirtide was incorporated into their ARV regimen. All patients remained on ARVs until 90 days post-transplantation. A significant HIV rebound was seen in a patient after ARVs were interrupted. HSCT has also been shown to functionally cure three patients with HIV(27,28)third is yet unpublished) who received HSPCs from C-C chemokine receptor type 5 (CCR5) null (CCR5 Δ 32/ Δ 32) homozygous donors; this is believed to be the consequence of preventing R-5 tropic viruses from binding to their target cells. The likelihood of SA being able to replicate this is very low as the prevalence of CCR5 null donors is far lower in patients of African descent than in those of European descent(29), and this is exacerbated by the fact that we have very few donors to start off with.

In the literature there is only one report of a D-indet (HIV antibody test) to R- HSCT.(30) Of note, the HIV ribonucleic acid (RNA) polymerase chain reaction (PCR) results on the donor remained negative. The HSCT was a success and the recipient's HIV test at 6 months was negative. Certainly, in our situation of a known donor LWH, the possibility of transmitting HIV to the recipient is very real.

HIV positive donor haematopoietic stem cell transplantation

There is no case in the literature of D+/R- or D+/R+ HSCT. We need to be pragmatic in our approach and consider all potential risks that recipients may be faced with, as discussed below. The ability of PLWH to tolerate ARVs and immunosuppressants as HSCT recipients is a good benchmark in considering post-transplant risk factors. Besides the risks described, consideration must also be given to the added cost of lifelong ARV treatment in the D+/R-

setting. As in D-/R+ HSCT, engraftment should not be affected in either D+/R+ or D+/R- HSCT. Recovery of T-cell subsets will have to be monitored and additional infections will have to be anticipated.

Whether the recipient is a PLWH or not, it may be useful to consider *ex vivo* T-cell depletion of the graft to reduce the HIV-infected CD4-T lymphocyte load. This would however require a CD34+ selection process which would add to the cost of the HSCT. Alternatively, *in vivo* T-cell depletion with PtCY can be considered as it would not only reduce GVHD but potentially, or rather theoretically, the risk of contracting HIV in R- transplants. Even if T-cell depletion is undertaken, the potential CD34+ haematopoietic stem and progenitor cell (HSPC) latent reservoir must still be considered. Whether HIV infects HSPCs remains controversial. HSPCs are known to express HIV co-receptors, CCR5 and CXCR4,(31,32) and investigators have suggested that HIV may latently infect HSPCs. Latent infection describes HIV which once integrated into the host genome, does not replicate, making it undetectable.(33). In some studies, evidence points to infection of a sub-population of HSPCs,(34,35) while in others no evidence of HIV infection has been found.(36,37) If the HSPCs are indeed infected, in the setting of HSCT, the transmission of HIV and the risk of viral resurgence from a viral reservoir is certainly a possibility.

The continuation of ARVs in a D+/R+ or the initiation of ARVs in a D+/R- HSCT represents a risk of drug interactions that must be anticipated prior to initiation of therapy. In SA, first-line ARV treatment consists of Tenofovir disoproxil fumarate (nucleoside reverse transcriptase inhibitor [NRTI]), Lamivudine [NRTI] and Dolutegravir (Integrase strand transfer inhibitor [INSTI]) in a fixed-drug combination tablet known as TLD.(31) Hypothetically, in D+/R+ HSCT this regimen (TLD) could be continued and in D+/R- HSCT, this could potentially be commenced in the recipient initially. In cases where patients are unable to continue with oral treatment, enfuvirtide (HIV entry inhibitor) can be used until oral treatment can be recommenced.(32) Maraviroc, a CCR5-antagonist, could be considered in the case of CCR5-tropic HIV in D+/R- HSCT. (32)

The haematological abnormalities observed in PLWH may be due to a combination of direct infection of HSPCs, an abnormal cytokine milieu and exposure to ARVs.(33,40) ARVs have however been shown to improve these haematological abnormalities, particularly anaemia and thrombocytopenia.(41) The potential effect on the HSPC (discussed above) and immune dysfunction as a result of ARVs are important to consider in the acute setting post HSCT.

PLWH are known to have an increased risk of developing lymphoma, some of which are acquired immunodeficiency syndrome (AIDS) defining cancers.(42) Although this risk is not entirely eliminated with ARVs, decreased rates of disease are reported. In parallel with this improvement, an increase in non-AIDS defining malignancies are now being seen.(43)This will have to be considered in the patient who could potentially contract HIV in a D+/R- HSCT.

D+/R+ or D+/R- transplants, as discussed above, are not without risk. However, this raises the question as to whether we can afford to exclude millions of potential donors as a consequence of their HIV status? In a virologically suppressed donor LWH, with normal haematological parameters and in the face of a patient at risk for a relapsing or rapidly progressing high-risk haematological malignancy, whether R+ or R-, careful consideration should be given to utilising this donor (D+). Particular emphasis must be placed on the consent procedure where all potential risks of the procedure should be carefully explained. Whatever the decision, it is highly likely that SA clinicians, as was the case when donors LWH were being considered for SOT, will have to be the drivers of this change.

Umbilical cord blood from HIV exposed uninfected (HEU) infants

The highest prevalence of HIV (20-25%) in SA is seen in females between the ages of 15 and 49 years and this increases up to an alarming 30-40% in pregnant women in some areas.(44)(45) Due to mass roll-out of ARVs in antenatal clinics, 96% of pregnant women LWH are on ARVs.(46) One of the greatest achievements of this endeavour has been to lower the early mother to child transmission (MTCT) rate, defined as preventing infection within the first six weeks after birth, which is currently at 1.1%, down from 3.5% reported in 2010.(45) ARVs decrease the viral load in the mother while simultaneously providing pre-exposure prophylaxis to the fetus. As MTCT pertains to UCB from HEU infants, the proportion of infections due to *in utero* HIV transmission is a critical consideration, and this is reported on average to be 0,9%.(45) The risk of in utero transmission of HIV is increased in mothers who are not virologically suppressed and in those who start ARVs within 4 weeks of delivery.(47)

In SA all babies born from mothers LWH must have an HIV PCR performed at birth.(31) This test remains very specific in detecting *in utero* HIV-infection(47) but some cases may be missed as those with *in utero* infection have lower viral loads due to ARV exposure *in utero* and early initiation of ARV prophylaxis.(48) Recently, the GeneXpert HIV-1 qualitative assay has been shown to improve the positive predictive rate of an “HIV-detected” PCR result when used as a consecutive test.(49) Further validation can also be performed by testing the UCB

for HIV RNA with the Ultrio Plus.(50) All of these factors together could greatly increase the confidence with which we declare these UCB units to be HIV-negative. Sero-conversion may however still occur post-delivery and how much of this is attributed to possible *in utero* infection is not clear. It may be feasible to monitor the patient for 1-year post banking of the UCB unit as an additional safety measure.

As a group, HEU children are also known to have worse outcomes compared to HIV-unexposed infants including sub-optimal growth, neurodevelopmental delay, congenital anomalies and increased infections.(51–53) The maternal cytokine milieu is altered in response to HIV-infection, and some of these abnormalities including increased interferon gamma (IFN-γ) and tumour necrosis factor (TNF), and decreased interleukins (IL)-4 and -7, are shared in infants born from mothers LWH.(54) In a study by Kroeze *et al*, C-X-C chemokine ligand 10 (CXCL10), lipopolysaccharide-binding protein, C-reactive protein (CRP), soluble CD163, and soluble scavenger receptor CD14 levels were found to remain elevated in the presence of ARV treatment.(55)

In considering the complications seen in HEU infants, much is attributed to ARV exposure and direct toxicity but there has not been a definitive answer as to whether HSPCs may also be affected and thus be a cause for some of these abnormalities. A comprehensive literature review included studies that compared the CB to maternal serum (C:M) concentration ratio of a number of ARVs.(56) In the majority of cases, NRTIs penetrate the placental barrier best with C:M ratios close to and even above 1, followed by non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Dolutegravir has also been shown to have a C:M of 1.2(57) A wide range of haematological abnormalities have been described in HEU infants, including anaemia(58), neutropenia(58) thrombocytopenia(59), lymphopenia(60) and reticulocytopenia(59). Drugs found to be particularly problematic are zidovudine (AZT)(61) and the combination of AZT and lamivudine.(58) In SA, AZT is used for post-exposure prophylaxis in infants of high-risk mothers where virological suppression has not been confirmed.(62)

One study showed impaired HSPC function in HEU infants with a marked reduction in the ability of UCB mononuclear cells (MNCs) to form colony forming units (CFUs) compared to an HIV-unexposed control.(63) It is important however to note that these investigations were not performed using isolated HSPCs but using UCB MNCs containing only a small proportion

of HSPCs. The impact of HIV exposure on isolated CD34+ HSPC function therefore remains unknown.

UCB HSPCs from infants of mothers LWH who are virologically suppressed, should thus be viewed as a different source category of HSPCs to HSPC donations from PLWH. It seems reasonable to suggest that the risk of HSPC infection is low, particularly if the birth HIV PCR result is negative, in conjunction with the HIV test on the UCB. Furthermore, follow-up testing on the infant confirming that they do not seroconvert would provide reassurance of the low risk of transmission of HIV from these UCB products. The potential problem here is thus not only the risk of HIV-infection itself but the impact of HIV on HSPC function, having been exposed to the cytokine milieu of the mother LWH as well as ARVs *in utero*. Considering all the above, could we potentially use these units for HSCT in SA?

A noteworthy consideration is that with the advent of haploidentical HSCT, the number of UCB HSCTs in children is slowly decreasing(64) This begs the question: should we be considering UCB as a SC source when usage globally is diminishing? Still regarded as a second line donor SC source, UCB does have the very important feature of allowing for less stringent HLA-matching.(65) The use of UCB requires matching at only 6 loci compared to the usual 8-10 loci. There are also additional very important advantages. The collection of these cells is non-invasive and risk-free for the infant, the likelihood of transmitting infections is decreased, it is immediately available when needed and there is less GVHD.(66) Viljoen *et al*. recently discussed the potential and need for the establishment of a public UCB bank in SA.(67) With a population as genetically diverse as SA and the potential to increase HLA matches, we need to consider this as a donor source. The potential inclusion of UCB units from HEU infants, which make up 30-40% of possible samples, may further increase the viability of such a bank. Additionally, expansion of HSPCs, an increasingly important strategy being pursued to overcome the limited number of HSPCs present in a single UCB unit, is also a possibility. Expanded SC products have been shown to lead to more rapid engraftment(68) overcoming the previous disadvantage of delayed engraftment/immune reconstitution, particularly in adults.(66) Molecules such as Stemregenin-1(69) and UM171(70) have been tested clinically in phase I/II trials with very promising results. The first patient with aplastic anaemia treated with a stand-alone UM171 expanded UCB graft, engrafted well with no serious infections.(71) These observations point to the potential use of an expanded UCB unit as a 'stand-alone-graft'. This will also potentially allow for banking of what is presently considered to be an 'insufficient' UCB unit due to low cell numbers, increasing the number

of available units.(72) The evidence for this is provided by Dumont-Lagace *et al.* who found that UM171 expanded UCB cells increased cord blood availability for African Americans from 53%-78%.(73)

Ethical considerations

Considering that all transplantations are only undertaken in the event of end-stage organ disease or a life threatening haematological condition, Wispelway *et al.* highlight that in D+/R- SOT "HIV retains an ability to inspire fear out of proportion to its effect on public health".(74) The authors describe (a) autonomy, which allows patients the opportunity to consider the risks of graft receipt whilst knowing the benefits, as all organ/HSPC transplantation is undertaken in the context of life-threatening disease; (b) beneficence, which may argue that doing good for a patient who will certainly die is a prerogative and overrides the potential non-maleficence in this case;(74) and (c), in considering justice, the wider social context and benefit must also be considered - more people could become HIV infected (in D+/R- SOT and HSCT); however, many patients who require transplantation would benefit and lives will be saved, with positive socioeconomic benefits. This decision is not without "psychological risk" and "biological risk"(75) as described in D+/R+ SOT, as we do not know what the outcome of such a transplant is expected to be.

The case of the liver transplant at WDGMC provides an important perspective on autonomy : "failure to offer parents LWH the option of donation to their HIV-negative children is an infringement of their autonomy".(76) This argument must be posed in conjunction with the autonomy of a patient who is able to consent, or parents of children who are unable to consent, who will have to decide on their own view of potential HIV acquisition in themselves/their child versus the risk of disease progression and even death.(12)

Conclusions

To ensure that we are prepared for what decisions need to be made in the realm of considering PLWH as SC donors, it is crucial that consensus is reached by the larger HSCT community. The SA adult and paediatric clinical haematology/oncology community and HSCT fields, together with SC laboratories performing *in vitro* research on HSPCs from PLWH, should meet and discuss a way forward.

We propose that each HSCT unit considering PLWH as donors set up an "HIV donor forum" composed of a multi-disciplinary team to address all medical and non-medical related

matters. The team should consist of a core medical team who will lead the forum and would comprise at least two SC transplant physicians who will outline the donor and recipient criteria to be adhered to for the transplant (see below). Potential questions to address are highlighted in Table 1. If both members of the core team are adult physicians, a paediatric haematologist or oncologist should also be included to ensure that specific matters related to paediatric transplantation are addressed. Second, a support medical team consisting of a SOT representative, with experience in transplantation in PLWH and an infectious diseases specialist, ideally having some experience in infectious complications related to HSCT in addition to HIV, must be established. A regulatory and ethics team would serve as advisors to the forum members on what ethical implications are to be considered in the introduction of an HIV-positive SC donor programme. Amongst other matters, they should define how the consent process should be different, including how often counselling should be undertaken in both the donor and the recipient. This team should also be the liaison between hospital management and the hospital ethics committee. Representatives of the patient, donor, and the parents in the event of either the patient or donor being a minor, must be included. Ancillary support staff including a counselling psychologist and trauma counsellor should be available. The former has a crucial role in ensuring the correct information and relevant risks are explained and understood in both donor and recipient. The latter is important in the event of a poor outcome in the recipient. This function may have to be performed by a team of psychologists. In the case of a paediatric recipient, the caregivers and any other relevant family members should be involved and prepared. Social workers will also enhance the process by ensuring sufficient support is available for the patient before and after the transplant. A scientific support team consisting of at least two scientists and/or clinician scientists with SC experience can provide support in terms of any *in vitro* scientific studies that need to be performed to enhance clinical decision making. Examples include *in vitro* experiments on the functioning of HSPCs from HEU infants and PLWH, such as CFU formation, followed by engraftment studies using the HSPCs from these donor sources in mice.

The core and support medical teams should review the available literature, and standardised guidelines should be developed to ensure maintenance of the principles on which these donors are considered.

Should any transplant centre consider such a donor, the case in question and all the processes followed should be documented and reviewed on a case-by-case basis. Ethics

approval should be obtained, and an institutional review board be created to oversee the regulatory aspects of the procedure, as was the case with the implementation of the HOPE Act.(13) The findings could be written up as a case report or case series to guide and encourage future discussion on the matter. The outcomes of these transplants should be reviewed by larger consortia on a bi-annual basis to ensure procedural consensus, after which national guidelines can be implemented.

Finally, as SC donor recruitment in SA increases, we will face the inevitable "HIV-positive/exposed donor to HIV-negative recipient" question. In high-income populations such as Europe and the US, where a much higher probability of finding matches exists in the context of areas of low HIV prevalence, this is unlikely to be considered. This will thus remain a sub-Saharan African problem, to be solved by sub-Saharan African clinicians. We also need to consider that UCB, because of its unique advantages, remains a donor source that cannot be ignored, and thus HIV-exposed UCB units will fall into the realm of what might be possible. In a society with high HLA diversity, where HLA matches are rare, all potential donors should be considered in order to improve access to HSCT. To prepare for such a situation, we need to engage as clinicians and stakeholders to determine what would make us comfortable to use these cells. Whether we prioritise PLWH who are virologically suppressed versus UCB from HEU infants may depend on pragmatic factors – the latter for example may require a more stringent pre-clinical work-up before we are comfortable with this potential source. Irrespective of what of these routes we choose, which, it must be emphasised, are not mutually exclusive, careful planning and execution could open up an important new resource for adult and paediatric patients for whom HSCT remains inaccessible due to lack of a suitable donor.

Search strategy and selection criteria

References for this Viewpoint were obtained through searches of PubMed using the search terms "HIV", "transplantation", "ethics of HIV transplantation", and "HIV-exposed uninfected infant". We considered all articles that were appropriate and relevant to our topic and published in English for our review.

Funding

This research was supported by the South African Medical Research Council (SAMRC), and the University Pretoria (to MP).

Declaration of interests

MSP is a co-founder and Board member of Antion Biosciences. Antion's proprietary technology is currently being developed to modify adult T-cells to target tumour cells. Our manuscript deals with haematopoietic stem cells derived from umbilical cord blood in HEU infants for the purposes of HSCT to replace HSCs in the bone marrow destroyed by chemotherapy, in order to reconstitute the haematopoietic system.

Author contributions

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