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Challenges in Medical Ethics:

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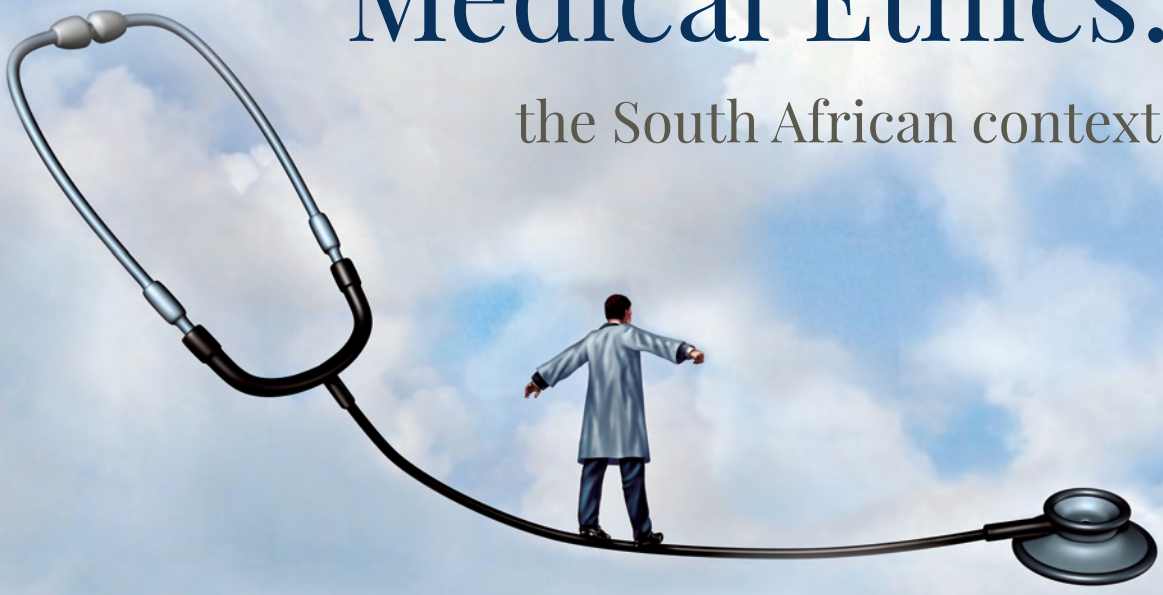

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6

Ethical Issues in the HIV-positive to Positive Transplant Setting

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Keywords: clinical decision-making; deceased donation; end-stage renal disease; evidence-based medicine; HIV; renal failure; transplantation

6.1 INTRODUCTION

This chapter is written from a personal perspective, highlighting some of my experience as a transplant surgeon while starting a programme to transplant HIV-positive patients with end-stage renal failure (ESRF) with kidneys that came from HIV-positive deceased donors. I would like to try and show the ethical issues which had to be considered before and immediately after the first transplants were done at the end of 2008.

When I started working in transplantation, my youngest son had just been born. Four years later, I met a patient to whom I will refer as Sarah.[1] I was particularly moved by her situation. She was a 29-year-old mother with a four-year-old boy – also the age of my son – who accompanied her to the renal unit. The child was a typical four-year-old who ran around and demanded his mother's attention while she was talking to me. The mother was a beautiful, kind, graceful woman. She didn't speak good English, so we used short sentences and made do with minimal vocabulary. After a while, I called a translator, our social worker who had first introduced me to the patient. He told me that Sarah had been diagnosed with HIV and renal failure at the same time, about three months before. She was not aware of her HIV status until she presented symptoms of ESRF and was

1 Fictional name.

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tested for HIV. After testing positive, the presumption was that she had HIV-associated nephropathy (HIVAN) as a cause of her kidney disease – something we used to see quite commonly in South Africa when antiretroviral therapy was not available to all patients with HIV. Sarah was turned down for dialysis. She was in the prime of her life, socially responsible in her duties of motherhood, in a good state medically except for HIV and renal failure. How could this happen, and what did it mean?

The second story is about a patient I will refer to as Peter.[2] He was 36, living with his older brother in Cape Town, selling sweets to make a living. They fled Uganda just before the 2006 elections when President Museveni was re-elected. Peter supported the opposition candidate in Uganda who had spent much of his campaign period in jail. After Museveni's re-election, Peter and his brother feared for their lives. Civil war, although it waxed and waned in intensity, had been an enduring aspect of life in Uganda for 20 years. When Peter came to South Africa, he applied for refugee status. Two years later, he was granted a permanent visa to remain in South Africa. Although he was struggling financially, compared to life in Uganda he was much better off. He and his brother managed to rent a small flat in Cape Town. Prior to 1994, immigrants from elsewhere in Africa faced discrimination and even violence in South Africa, though much of that risk stemmed from the institutionalised racism of the time due to apartheid. After democratisation in 1994, contrary to expectations, the incidence of xenophobia in South Africa increased. Peter still feared for his life every day in South Africa. Struggling to make ends meet, he and his brother worked tirelessly to continue to afford their accommodation in Cape Town. They were too scared to move to a cheaper area or township, as they could speak none of the native South African languages.

In July 2008, Peter started to feel unwell. He was tired, short of breath, and felt very stressed. He was wondering whether the psychological burden of living in dismal circumstances was affecting him. His brother accompanied him to the emergency room at Groote Schuur Hospital (GSH), where he was turned away as he did not live in the catchment area for GSH. After being told to go to the GF Jooste Hospital's outpatient clinic, he was seen a week later and diagnosed with HIV and ESRF. He was referred back to the GSH renal unit (the only state dialysis unit in a 30km radius for Cape Town) – and was presented at the Renal Unit Assessment meeting early in August 2008. At this stage, his creatinine was climbing – he was not feeling well, and his legs were permanently swollen. Having survived civil war and political persecution in Uganda and xenophobic violence

2 Fictional name.

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and structural racism in South Africa, Peter was turned down for dialysis. He was just one of many patients in category 3 – deemed unsuitable for transplantation – who would be turned down that week.

Again, I ask the question: How could this happen, and what does it mean? I will try to make sense of the predicaments these two individuals found themselves in, and the ethical choices provoked by their respective plights.

6.2 THE ECONOMY VERSUS THE "ETHICS OF POSSIBILITY"

In his essay, "Ethics: An Essay on the Understanding of Evil", the French philosopher Alain Badiou (Badiou, 2001) writes:

> There is no ethics in general. There are only – eventually – ethics of processes by which we treat possibilities of a situation. There is not, in fact, one single Subject, but as many subjects as there are truths, and as many subjective types as there are procedures of truths. The modern name for necessity is, as everyone knows, 'economics'. The logic of Capital. It consists of turning the spectacle of the economy into the object of an apathetic public consensus.

I want to use Badiou's radical perspective on ethics, his "ethics of processes" and the "possibilities of the situation" as opposed to the inertia of ethics as ideology to outline some of the choices I had to make in Cape Town, South Africa, when I started the world's first HIV-positive to positive transplant programme in 2008.

Constituted as subjects by the truths of their personal histories, fears, and ambitions, neither Sarah nor Peter was looked upon as viable economic projects – Badiou's "logic of capital" – in the truth of hospital or Department of Health budgets. Although the circumstances of both individuals strongly affirmed their subjectivity through their choices – the caring mother, the resilience to live – both came up against the logic of a system in which money decided what can and cannot be done to save their lives.

Like physicians the world over, we were forced to think of our vocation as Badiou states, "a bureaucratic medicine that complies with ethical ideology that depends on 'the sick' conceived as vague victims or statistics". Of course, other than point out that this is what happens when patients like Sarah and Peter test the possibilities of inadequate health care provision in developing countries, I cannot suggest easy solutions to the intractable problems of 'managing' health care from considerations that are radically external to genuinely medical situations. What I will do with the help of Badiou is suggest how being faithful to the genuinely medical situation – as opposed to the bureaucratic and managerial

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situation – enables doctors to treat the clinical situation as one that is faithful to the notion of an affirmative humanity as opposed to one based on humanity as statistics. Importantly, I argue here through these case studies and my subsequent programme of transplanting patients with HIV, that it is when doctors allow themselves to be overwhelmed by urgent, singular situations of need, that ethical decision-making happens.

6.3 THE ISSUE OF SCARCE RESOURCES

As a transplant surgeon in a relatively small unit at GSH (we did about 60-70 kidney transplants per year), I was called for every potential deceased donor and recipient in 2008. Generally, the transplant coordinator would phone me when consent had been obtained from a deceased donor's family and I would then be asked to get the preservation fluids, ice box, and instruments ready that we need to go and do the procurement operation. Sometimes the donor was in my own hospital, sometimes I had to drive to one of the peripheral hospitals, and sometimes I had to fly to, for instance, the Eastern Cape or Northern Cape, to do the procurement.

During preparation, the blood results we needed for the transplant would become available and I would be continually updated on these results. In 2008, HIV was a contra-indication to being a donor or to receive a transplant in South Africa, and should it happen that the donor's results would show that he/she was HIV-positive, we would decline that donor for transplantation. We would inform the family that some tests indicated that we could not use the organs. We would not necessarily disclose the HIV status of the donor to the family – only if he/she had a wife/husband or partner: where we felt from an ethical point of view the person needed to know the status of their loved one. Between 2005 and 2007, I declined many potential donors who were HIV-positive.

Of course, transplant surgeons work very closely with general nephrologists, who are the professionals who make the medical decisions related to transplantation. Like all medical professionals, general nephrologists in state hospitals in South Africa have to take into account policy that enables collective responsibility and allow them to make life and death decisions every week. In weekly meetings, all sorts of decisions will be taken about patients with renal failure. Nephrologists have to accept, every week, that patients cannot be treated at our hospital because they do not meet the medical/procedural requirements for dialysis. The reasons we have medical criteria are less medical, and more economic. Patients are classified according to three categories (Moosa, Meyers, Gottlich & Naicker, 2016):

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Category 1 represents the perfect transplant candidate: no end organ disease, no social concerns, no cardiac or chronic problems – basically an otherwise perfectly healthy and socially adjusted patient with end-stage renal failure. These patients will be acceptable dialysis patients. They will also possess the necessary legal residency papers and contribute to the South African Revenue Service. For every one patient in this group, there will be five patients (or sometimes more) who are classified as either category 2 or category 3.

Category 2 patients are those with a well-controlled additional disease besides renal failure. This could potentially be a patient with hypertension, asthma, well-controlled psychiatric problems, etc. However, this patient would only receive dialysis if there were a vacant place on our programme. With 300 dialysis slots serving a population of ±2 million people, the odds were stacked against even category 2 patients receiving dialysis. But in 2008, when I met Sarah and Peter, HIV was classified as a category 3 disease. In our context, this meant 'untransplantable'. I say 'in our context', because patients seen as 'not fit for transplantation in the South African context' would qualify for transplants in other places. These patients included type 1 diabetics, HIV-positive people, and people who did not attend follow-up and was stamped non-compliant. It would also include the teenager who experimented with drugs or alcohol when they were 16. In South Africa, if you were in this group and presented with renal failure, you would be sent home to die. In short, nephrologists' tasks in state hospitals in South Africa included decisions on which ill people in the South African medical system were to be treated, and which – because the budget and public opinion demanded it – were to be sent away to die.

Coming face-to-face with Sarah and Peter in 2008, I made a decision to respond to the needs of these individuals instead of the exigencies of the health care situation and how it had been set up to make Sarah and Peter into statistics. As a mother of a four-year old myself, I could not regard the beautiful Sarah as a category 3, or a category anything. To me, she was a mother with a child who deserved to live. Similarly, Peter, with his determination to live and to make a living, was an extraordinary individual rather than an anonymous category.

Meeting these individuals, I took the decision that I would investigate using HIV-positive deceased donor kidneys to transplant HIV-positive recipients turned down for dialysis in Cape Town. It was a decision that would change their lives, and mine. Before I return to a consideration of the ethics of my decision, and to make any consideration of this decision as an ethical one possible, it is necessary that I make a rather lengthy detour and explain the background to the HIV crisis in South Africa, the implications of this crisis for patients requiring

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transplantation, the medical risks of transplanting HIV-positive patients, the way in which we addressed these risks by our selection of donors and recipients, and the status quo of the programme.

6.4 THE BACKGROUND IN SOUTH AFRICA AND WHY THIS PROBLEM NEEDED TO BE ADDRESSED

South Africa has a large group of patients who are HIV-positive. The incidence of HIV in South Africa is two to ten times higher than in the rest of the world (Shisana, Rice, Zungu & Zuma, 2010). For a long time, the political climate in South Africa was one of denial and most politicians denied the impact that this virus had on the country. In Thabo Mbeki's opening address to the 13th AIDS conference in Durban, he pleaded with scientists to respect "the politician's point of view" (Horton, 2000). He acknowledged that South Africa has a health crisis of enormous proportions and concluded: "we cannot blame everything on a single virus". He emphasised that the world's biggest killer and the greatest cause of ill-health and suffering across the globe (including South Africa) is extreme poverty.

When the HIV-positive to positive programme was started, South Africa had 50.5 million people of which 5.38 million people were HIV-positive. In people between the ages of 15 and 25, the incidence was even higher: 21% of our population (Connolly, Shisana, Colvin & Stoker, 2004). These statistics were based on antenatal clinic statistics in the country as we do not have a register for HIV in South Africa. Important to note is that a large part of our population (84%) have no medical insurance and depend on the state for their health care (Mayosi & Benatar, 2014). It is this group of patients that was severely affected by the policies around HIV and renal care in the country.

In 2008, the situation was as follows:

1. Antiretroviral therapy (ART) was now available since four years ago;
2. The number of people on treatment grew rapidly, but not rapidly enough with only about 12 000 people on treatment by the end of 2006; and
3. In all state hospitals across the country, HIV-positive patients were declined for dialysis programmes.

A major problem is that a large percentage of HIV-positive people will develop HIVAN – HIV-associated kidney disease – the classic kidney disease associated with HIV infection. Working with the statistic of a 20% incidence of HIV in the country, we can reason that 1:5 people in the country has HIV. HIVAN will

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develop in approximately 20-27% of the untreated population and 8-22% of the treated ones (Banu, Banu & Saleh, 2013; Wearne et al., 2012). This means a conservative estimate would be that 1 in every 5 HIV-positive patients will develop HIVAN.

Histologically, HIVAN is a collapsing form of focal sclerosing glomerulosclerosis (FSGS), which can be distinguished from idiopathic FSGS by the presence of microcystic tubular dilatation and interstitial inflammation (Okpechi et al., 2011). HIVAN classically presents with proteinuria, but it seldom develops in HIV-positive people who are treated correctly and where the virus is controlled from a very early stage. Therefore, one can reason that HIVAN is the direct result of our health care system failing HIV-positive patients.

6.4.1 Options for HIV patients with renal failure in the South African context

The question in 2008 was what to offer these South African patients who were dying of renal failure. For medical practitioners, there were a few options available:

1. Continue to let the HIV-positive people with ESRF die;
2. Increase the available dialysis slots to treat more HIV-positive patients with renal failure;
3. Use HIV-negative deceased or living donors to transplant HIV-positive patients (as had been done in the USA); or
4. Utilise a new unique source of donors that has never been used before, the HIV-positive donor.

All four of these options had a unique set of ethical and logistical problems.

6.4.1.1 Continue to let the HIV-positive people with ESRF die

In a context with limited resources and a huge demand to provide primary health care, this was by default the position physicians, surgeons, and society found themselves in. By not accepting HIV-positive patients into renal replacement programmes, we managed to maintain a degree of stability in a crisis situation. Because dialysis had limited availability, HIV was one of the clearcut ways to lower the burden on this treatment option. Interestingly, because of the stigma the disease carried, the fact that very few patients in South Africa were prepared to make their HIV status known and the reality that HIV-positive patients were generally poor and had limited access to resources like the media, this 'status quo' situation was never questioned and never debated.

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6.4.1.2 Increase dialysis slots to treat HIV-positive patients with renal failure

Before 2008, but also in the subsequent years in Cape Town, dialysis slots remained stable or increased only marginally (Moosa, Meyers, Gottlich & Naicker, 2016). In terms of the population with ESRF, dialysis remained a totally under-resourced utility. In the state sector, which serves 75% of this population, we only have about 300 dialysis slots in the larger Cape Town area. Increasing these slots would in all likelihood have had a small impact on the treatment of the HIV population as such, as there was a huge need for both HIV-positive as well as HIV-negative patients for dialysis.

Furthermore, data confirmed that HIV-positive patients did not do as well on dialysis as with a transplant (Morales Otero, Molina & González, 1991). In a study done to compare dialysis and transplantation in HIV-positive people, transplanted patients had a much better outcome in terms of life expectancy as well as quality of life, compared to dialysis.

6.4.1.3 Using HIV-negative donors

The USA had been using HIV-negative deceased donors for transplantation into HIV-positive recipients with excellent graft and patient survival rates for about five years before 2008 (Roland et al., 2008). Rejection and infection rates were higher than for HIV-negative counterparts, but in general results compared with high immunological risk HIV-negative recipients. Transplanting HIV-positive patients with HIV-negative kidneys was a very safe option. The results from the USA were encouraging and although this would have been an easy solution, in South Africa it was also a very impractical one. Because of a severe shortage of deceased donors, the impact of this procedure on the HIV-negative waiting list would have been dramatic. Not only would the small number of deceased donors in the country have had to be shared with a new and quite large group of HIV-positive patients, but the unutilised source of donors, namely the HIV-positive donors, would also remain a lost resource.

Using HIV-negative living donors for recipients who would seem to be higher risk patients for infective and rejection risk than the average HIV-negative patient did not seem ethical or responsible at that stage. Living donation should only take place in circumstances where outcomes of recipients had already been researched and proven to be optimal.

This made the use of living or deceased HIV-negative donors for HIV-positive recipients morally and ethically questionable in a country where there was no experience yet with transplantation for HIV-positive patients.

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6.4.1.4 Using HIV-positive deceased donors

In a country where many referred braindead patients were found to be HIV-positive, it made sense to try and think about a way to incorporate this pool of potential deceased donors into the pool of confirmed or utilised deceased donors. But certain questions needed to be asked first and the most important was: What will happen when you introduce a second viral strain into an HIV-positive patient by transplanting a kidney from an HIV-infected donor? There was no transplant model for this, so when I started the programme, I reviewed the literature that reported on sex workers who obtained a second viral strain through intercourse. The outcomes and reports of these HIV-positive patients with super infections were difficult to interpret as there were many methodological difficulties that often yielded conflicting results (Pernas et al., 2006; Smith et al., 2004).

The different types of dual infections might depend on the timing of the introduction of the second viral strain. When a patient with low viral load is exposed to a second viral strain, a superinfecting strain may be detectable for only a short period of time. Viral fitness and the ability of a viral strain to replicate effectively in a given environment may play a role to determine whether the two different strains will eventually become undetectable in standard resistance tests or whether outgrowth of a different virus from the baseline or a novel recombinant virus will become detectable. Judging the situation after a transplant would rely on this data.

In 2008 in South Africa, we had a unique situation because we had low ART resistance rates. Most patients who failed second-line ART in South Africa had wild-type virus and resistance rates remained less than 5%.

Observational studies suggested that after four and eight years' access to ART in the Mankweng and the Bela Bela communities respectively, drug resistance mutations in the native population remained low (Nwobegahay et al., 2012; Waters & Smit, 2012). With this information available, the suggestion was that the risk for transplanting a resistant second viral strain was low in the South African context.

Utilising HIV-positive deceased donors made sense in our context (Muller, Barday, Mendelson & Kahn, 2012). Using deceased donors did not expose an HIV-negative living donor to a risky operation in a population group where we did not have significant experience in transplantation in South Africa yet. And using this group of donors opened up a new stream of potential organs that could never be utilised before. Besides this, the risk with this in the South African context seemed low because of our low viral resistance rates and fairly

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homogenous subtype C virus throughout the country. In 2008, looking at the literature and at outcomes after a second viral strain had been introduced to an already HIV-positive patient (for instance through unprotected intercourse), we knew that these patients could potentially get a flare up of viral load, or possibly a new recombinant virus. But one could argue that we didn't know how patients would behave in the kind of controlled circumstances of a transplant, a situation where we could time the introduction of the second viral strain and where viral load could be monitored closely following the procedure. We anticipated the virus to be completely suppressed by ART immediately after transplant and did not anticipate a flare up or a new recombinant virus. One could therefore argue that there was no evidence that this situation would be harmful to the patient. But there was also no evidence that the situation would not be harmful to the patient.

6.5. THE ISSUE OF RISK WHEN TRANSPLANTING HIV-POSITIVE PATIENTS

6.5.1 The risk of rejection

Rejection rates in the HIV-positive population are about three times higher than the HIV-negative population. Acute allograft rejection is associated with impaired long-term survival because of the increased risk of developing chronic rejection and it is estimated that the impact on long-term graft survival is to decrease the allograft half-life by 34% (Stock et al., 2010). Two major issues are probably associated with high rejection rates in this population. One is the dysregulated immune system that HIV-positive patients have, and the second is the challenge of managing the drug interactions between the antiretrovirals and the immunosuppressants. Many of the antiretrovirals either induce or inhibit the cytochrome P450 liver enzymes resulting in the need for either very high doses or very low doses of immunosuppression. Managing these drug interactions require regular trough levels and even slight dose modifications might change the exposure of the patient to immunosuppressive drugs. This results in higher rejection rates than in patients with less complicated drug regimens as highlighted in the next section.

6.5.2 The risk of drug interactions

Drugs can influence the cytochrome P450 enzyme in two different ways. First, the inhibitors of this enzyme will decrease the metabolism of substrates and generally lead to increased drug effects. This is the result of the inhibitor competing with the other drug for the enzyme-binding site.

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Second, the inducers will increase the metabolism of substrates and therefore lead to decreased drug effects. Thus: inducers will either stimulate more enzyme protein or enhance the enzyme's binding capacity.

There are some antiretroviral drugs in both these two groups (inhibitors and inducers) (Frassetto et al., 2003). Ritonavir is a strong inhibitor resulting in a five-fold increase in the drug exposure and an 80% or more decrease in clearance of the drug. Evafirenz and Nevirapine are both inducers of the cytochrome P450 enzyme, needing higher doses than normal of calcineurin inhibitor to obtain the same drug concentrations than in HIV-negative people.

When we started the HIV transplant programme, we switched a lot of patients to a Ritonavir-based drug regimen. The reasons for this were that

(a) it would reduce the amount of immunosuppressants needed dramatically and result in a much cheaper regimen of drugs; and

(b) Ritonavir-based drug regimens were second line treatment in South Africa and therefore it meant that the new incoming viral strain would be very likely to be suppressed if it was exposed to first line treatment in the past.

However, the side effects of the calcineurin inhibitors become more pronounced and some patients on this regimen developed features of calcineurin toxicity on their biopsies. This resulted in a poorer graft survival in some patients.

6.5.3 The risk of induction therapy

Because of the very high overall rejection risk HIV-positive patients have, all patients in our group receive induction therapy with Thymoglobulin (Sawinski et al., 2017). Thymoglobulin is a T-cell depleting agent that is efficient in both blood and peripheral lymphoid tissue because of complement-dependant cell lysis. The effect of the Thymoglobulin induction therapy on the CD4 count is very dramatic and lasts a long time. The median CD4 counts in our study group has dropped from 340 (with an interquartile range of 324 to 511) as measured on the day of admission to 180 (with an interquartile range between 172 and 516) as measured at one year (Muller et al., 2020).

In the next few years after the transplant, CD4 counts do recover and all patients have an upward trend after their transplant.

Weighing up the risk of acute and severe rejection at the time of the transplant versus the long-term well-being and risk for infection over the next few years was a very difficult clinical decision. Informed consent meant that patients should be made aware of the use of lymphocyte depleting medication and the

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long-term side effects of the drug. As most patients knew they would die if they did not get renal replacement therapy, the choice was fairly easy for them. However, as the treating physician, the decision to prevent rejection in a way that was not possible to revert was difficult. Guided by the experience in HIV-positive patients who received HIV-negative kidneys in the USA, and their very high rejection rates, a decision was made to use induction therapy and to follow-up patients very carefully after the transplant. The result was that patients were required to come to a weekly post-operative clinic for the first three months and that several prophylactic agents were used to prevent infection with tuberculosis, pneumocystis, and viral and bacterial infections as I will highlight in the next section.

6.5.4 The risk of infection

Opportunistic infection is a general risk when you receive a transplant, even with minimal immunosuppression (Muller, Barday & Kahn, 2015). If you are HIV-positive, receive Thymoglobulin, and are maintained on fairly potent immuno-suppression, the risk for infection increases. Therefore, all HIV-positive patients need prophylactic therapy to prevent opportunistic infections.

This includes lifelong antibiotic treatment for pneumocystis pneumonia, lifelong isoniazid to prevent tuberculosis as well as Valganciclovir for three to six months to prevent cytomegalovirus infection. Patients therefore not only sign up for immuno-suppressive drugs with potential side effects, but also for several antibiotics and antiviral drugs, resulting in a large medication burden. After a transplant there has to be careful patient education so that people don't get overwhelmed with the pill burden.

As a result of this post-operative infection risk, this patient population needs constant monitoring for urinary tract infections, respiratory infections as well as serious opportunistic infections like tuberculosis and meningitis. During the Covid-19 pandemic, there were four patients in this transplant cohort who died before the vaccines were made available. Even after the vaccine was on the market, Covid-19 remained a serious risk to immunosuppressed patients as their response to a vaccine was limited because of a reduced capacity to make antibodies because of their immunosuppression. Patients needed third doses of Pfizer and second doses of the Johnson and Johnson vaccine before any immune response was noted.

The decision to receive a transplant does have long-term effects on your health and carries the risk of infection. This is the reason why a careful conversation, weighing up these sometimes even unknown future risks with the risk of not

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receiving a transplant takes place. (We did not even think of a pandemic like the recent Covid-19 pandemic when we consented patients in the past.) In the case of kidney failure and no access to dialysis, this decision is fairly logical. However, if there are options for treatment outside of this scenario where a patient is doomed to die, the ethical argument becomes less clear.

6.5.5 The risk of the second viral strain

When the transplant programme started in 2008, there was no way to be sure that the introduction of a second viral strain would not cause a flare up of viral load or a recombinant new virus that might be resistant to ART. For the first year, all patients received regular monthly viral loads post transplantation. If a viral load would flare up, the plan was to switch the ART, although some of the new classes of drugs were not yet available at that time. We saw no patients with detectable viral loads after the transplant and we also saw no patients who had a flare up of clinical problems with the new HIV strain post-operatively. This was very reassuring.

During 2014, we started doing a detailed sequencing of all donors and recipients to look at the viral strain for each patient (Selhorst et al., 2019). It was technically very difficult to do as the recipients had undetectable viral loads because of the ART they received. However, we found no patients where the virus changed and reported these results in 2019. As time went on, it became easier to reassure patients about the safety of using HIV-positive donors. It is also because of the scientific work we reported, that policy to use HIV-positive donors changed in other countries, like the USA.

In 2017, the Hope Act was signed by President Obama in the USA and, since then, HIV-positive donors could be used in this country as well. Before this time, it was prohibited by law. Similarly, policies changed in England and Europe, resulting in many places now offering HIV-positive donors to HIV-positive recipients (Durand, Segev & Sugarman, 2016).

6.5.6 The risk of death

Not only do patients need to be informed about infections and rejection when receiving a transplant, they also need to know that if severe opportunistic infections occur, there is a risk of death (Muller, 2015). Most patients in this study faced death in any case, because of the general lack of dialysis slots. Even after dialysis policies changed and HIV patients were allowed to dialyse, there was still a limited number of patients who could be helped because of the resource constraints in South Africa.

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Several incidences of death occurred in the study group (Muller, Barday, Mendelson & Kahn, 2015). One patient died one month after transplant when he became septic with chronic pancreatitis as well as a duodenal perforation. A second patient had recurrent gram-negative septicaemia due to recurrent urinary tract infections and grew a carbapenem-resistant klebsiella pneumoniae on blood culture. Another example of a patient who died four months after his transplant was a 45-year-old male who developed rapidly progressive invasive aspergillosis of his lung. These are examples of patients who died early after transplant and where the immunosuppression resulted in a very high risk for invasive infection.

There are also examples of patients who died later after a transplant. Some of the causes of death was unrelated to the immunosuppression, for instance a myocardial infarction and a metastatic squamous lung carcinoma.

When using potent immunosuppression, the risk of death should be considered and therefore any patient who consents to this treatment should be fully informed about this risk. This complicated discussion should also take place with family members, if possible, as many patients are not able to fully comprehend this risk when faced with a decision like this.

6.6 SELECTION PROCESS FOR DECEASED DONOR ORGANS

How did we select donors? We tried to select them according to the lowest possible clinical risk for a donor-derived disease or illness in the recipient (Muller & Barday, 2018). In other words, donors were chosen to minimise serious harm to the recipient, keeping in mind that the *potential* risk of harm to the recipient should be kept as low as possible. What is unique in this argument was that we accepted that there would be some risk to recipients, who were informed about this risk. In a world where patients as consumers are used to demanding a risk-free environment, this was perhaps unique.

One could argue, however, that this was not that different from using a marginal donor for a recipient and discussing this in the informed consent. Or when one buys a generic medicine, and you know that this preparation is not the one tested in the laboratory as part of the original research. A generic drug product is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use, but it is not exactly the same. To bring a generic drug into the market, bioequivalence needs to be shown, but nothing more. Thus, consumers buying this product do so in the full knowledge that they are buying a cheaper alternative, willingly accepting the complications of this choice should there be any. In the case of

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using a marginal organ, the patients as consumers can make this same decision if they are fully informed about the risk.

In the South African study, we selected our donors to be either naïve to ART or on first-line treatment with no sign of resistance. Later on in the study, we could do more tests to prove if a donor was on ART by using mass spectrometry. However, when we started, we relied on the clinical records of the patient to make this decision. We also wanted the donors to have a normal serum creatinine. Sometimes braindead patients had a temporary spike in their creatinine level because of the trauma or short-term issues with acute tubular necrosis of the kidney at the time of death. However, there was usually a record of a fairly normal creatine before the time of death which could guide us about the long-term well-being of the donor's kidney. We avoided donors with significant proteinuria as this was a possible sign of damage to the donor kidney by the HIV he or she had as well. As we did protocol biopsies on reperfusion of all the transplanted kidneys, we learned a lot about the assessment of the donor through the years and we also noted that HIVAN sometimes improved when on the correct treatment. There were some biopsies that showed mild signs of change as a result of the donor's own HIV and with time these changes disappeared and gave no clinical problems.

To avoid any donor-derived infection in the recipients, we did not use anyone who had an active viral, fungal, or parasitic infection as a donor. We also avoided using a donor with any malignancy.

6.7 A REFLECTION ON THE HISTORIC EVENTS IN VIEW OF CURRENT RESULTS

Until today, we have done almost 60 HIV-positive transplants from HIV-positive recipients and have published our results at several time points over the years.

The cumulative patient survival at one year is almost 90% and this is compatible with higher risk HIV-negative recipients. There are some patients who lose their grafts because of chronic rejection resulting in a one-year graft survival of around 90% as well. Overall, the outcomes are such that we have continued to use HIV-positive organs for HIV-positive recipients without any problems.

Looking back at September and October 2008, when I transplanted the first four HIV-positive patients with HIV-positive kidneys, I also want to keep my first two patients, Sarah and Peter, in mind. The reaction from the hospital and the provincial administration was to impose a moratorium on HIV-positive to positive transplant procedures. I was asked to submit a formal study protocol to the University of Cape Town's ethics committee and to get separate funding and

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support for this study to continue. I was asked to do a detailed cost analysis, look at the impact of these patients on dialysis slots and report back to the provincial Department of Health. I also received a disciplinary warning for flouting the policies and procedures of the Western Cape Provincial Administration.

Over the next 12 months, my professional and personal life were dominated by the fall out of my decision to transplant Sarah, Peter, and two more patients with HIV-positive kidneys. The institutional response to these transplants was, in many respects, quite brutal. And yet, two years later, as a result of these transplants, the dialysis policies in the Western Cape were changed. Doing the transplants had changed the basis of argument, the conditions of possibility for these procedures.

Badiou would say: Being faithful to the fidelity of a truth process, by linking the known (that these patients would die without the procedures) to the unknown (what would happen if they were transplanted) and by persevering in addressing this unknown. HIV patients were accepted into the state dialysis programmes. They became not only eligible to receive HIV-positive organs, but also HIV-negative organs. In August 2009, the HIV-positive to positive programme could be restarted.

During the period of the moratorium, four HIV-positive patients with ESRF died because I was forced to decline the use of four kidneys. While I was being disciplined and investigated for transplanting four patients who would have died and were now leading healthy lives, no one was held accountable for these deaths, even though they were preventable.

6.7.1 Who decides what is the right thing to do?

Alain Badiou writes about the constitution of a subject, a becoming-subject through truth processes that depose constituted knowledges and thus opposes opinions (Badiou, 2001). These opinions, he writes, are representations without truth, the anarchic debris of circulating knowledge. In practice, I understand this to mean that certain situations, if they are approached as consistent encounters with other subjects, hold the power to expose patterns of thinking or behaviour as limited. Badiou would probably say 'evil', but I would hesitate to go so far. Thus, the truth of life for Sarah or Peter exposes the anarchic debris of constituted knowledges circulating as policies born of fear and neoliberal economic common sense. And yet, it is important for me to reflect what the opening up to such encounters could mean practically, and not only philosophically.

The situation in which I performed my transplants in 2008 involved many parties: a conservative medical community, a larger university community consis-

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ting of ethicists and philosophers, policymakers, administrators, the community of HIV-positive patients, and the community of patients with renal failure. This was a situation where the system uncertainties were high and where epistemological and ethical issues were multiple. In these circumstances, the traditional domination of hard facts over soft values often gets inverted. In this situation of a high level of uncertainty, approaching sheer ignorance, I realised that I would never be able to solve the situation unless I simply jump in. Not on the basis of hard facts, but on the basis of personal need of each and every individual patient.

My first enquiries to the university ethics committee about my idea of using HIV-positive donors for HIV-positive recipients, elicited the following two responses:

> … I see this as therapeutic care in this population and not research …
>
> … off label use of medicines and procedures fall under the responsibility of the clinician …

This seemed to put me in the clear to proceed. I did not plan these transplants as research when I started – I was simply trying to increase the organ donor pool. Therefore, it seemed to me that my plans were similar to the clinical decisions we had to make when using donation-after-cardiac-death donors, older donors, and donors with other infections that could potentially flare up in the recipients.

But after I had performed the transplants, the hospital authorities and some of my colleagues no longer accepted these arguments. So, the programme had to be submitted as a study and all the consent forms and protocols reviewed by the University of Cape Town Research Ethics Committee. I was initially informed that the transplant programme would only be acceptable if the patients could also get access to dialysis. Providing transplantation without a dialysis programme, the argument went, would be unacceptable from an ethical point of view. The reasoning here was that patients who receive a transplant that for instance did not work, should be able to fall back onto dialysis. There was also the assumption that only patients who have access to dialysis could safely consider the risk that a transplant with an HIV-positive donor would hold. I was therefore asked to facilitate discussions in the state sector to make dialysis accessible for HIV-positive patients and also to ensure that HIV-positive patients were listed on waiting lists for HIV-negative donors. It was made clear to me that it would only be acceptable to enrol patients into the study if they were willing to take an HIV-positive kidney as an alternative form of treatment to either an HIV-negative kidney or dialysis. This basically left me in a position where I could, in the next few months, only accept patients who were able to access dialysis in the private sector but chose to accept an HIV-positive kidney on my programme. As dialysis policies took another six to twelve months to change in the state sector, I was

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unable to transplant any state dependent patients during this time. HIV-positive people were only accepted for state dialysis programmes at the end of 2009.

To my way of thinking as a surgeon who saw people die because of the time it took for these decisions to be taken, the timing and pace of change became a very real part of the process of ethical decision-making. What would be for Badiou the *event* that effects a break from a particular order of doing things, has a temporal dimension. It is not, in other words, all the same to the individuals concerned whether changes happen fast or slow. It is this temporal dimension of decision taking, the event that forces the break in the situation, that needs to be closely scrutinised not only for its ethical implications, but for the structural understanding it allows of the complexity of ethics.

In *The New Yorker* of 29 July 2013, Atul Gawande writes about slow ideas (Gawande, 2013). Why is it that some ideas spread swiftly, and others spread slowly? He uses the example of Bigelow and Morton's discovery of ether and chloroform reported in the Boston Medical and Surgical Journal in 1846 versus Lister's innovative idea of carbolic acid for cleansing which resulted in lower rates of sepsis and death published in *The Lancet* a few years later in 1867.

The idea of a painless anaesthetic spread like a fire and within a year the whole of Europe and large cities in the rest of the world adopted these new anaesthetic practices. However, it took a whole generation to implement aseptic technique as suggested by Lister. The author then proposes that the visible and immediate problem of pain forms a stark contrast with the invisible problem of germs. He also proposed that both these practices made life easier for patients, but that only one made life easier for doctors. Listerism was tedious; the dilution he suggested burnt surgeons' hands and asked a sacrifice from the surgeon. So, he proposes that it is for this reason that behaviour took so long to change.

In my case, changing the criteria for dialysis and transplantation to benefit HIV-positive people would make things difficult for the nephrologists who need to constantly worry about the budget of state hospitals and furthermore it would make it impossible for the health care system as they would suddenly have to cope with a new set of patients accessing the health care facilities. In one meeting with a state official, I was told "transplantation is of no benefit to us – every patient you transplant opened up a new slot on dialysis and now we have to pay for two patients – one on immunosuppression and a second new one on dialysis".

In this complex system where it was unclear where control was located (the university, the clinical peer group, the ethics committee, the provincial administration, the courts) and unpredictability and contradictions therefore multiplied, I had

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to ask myself: Can I solve this problem with the traditional problem-solving strategies like going back to core science and applying it, or by simply relying on professional consultancy? Badiou (2001) answers the question as follows:

> To be faithful to an event is to move within the situation that this event has supplemented, by *thinking* (although all thought is a practice, a putting to the test) the situation 'according to' the event. And this, of course – since the event was excluded by all the regular laws of the situation – compels the subject to *invent* a new way of being and acting in the situation.

Key here is the notion of inventing new ways of being and acting in situations that require immanent breaks in processes through the sheer intractability of the paradoxes and unpredictability resulting from the complexity conditions. Where applied science is mission orientated, professional consultancy is client serving. Where core science is curiosity motivated, the situation created by the dire medical prospects of Sarah and Peter was issue driven. A policy for HIV-positive patients could therefore not proceed on factual predications, as there were none. But the impact of these transplants would be universal, long term, novel but also complex and variable. Facts were uncertain, values were in dispute, stakes were high, and decisions were urgent as patients were dying.

In his essay on ethics, Badiou actually writes about medical ethics:

> […] there is only one medical situation, the clinical situation, and there is no need for an 'ethics' (but only for a clear vision of this situation) to understand that in these circumstances a doctor is a doctor only if he deals with the situation according to the rules of maximum possibility – to treat this person who demands treatment of him as thoroughly as he can, using everything he knows and with all the means to his disposal, without taking anything else into consideration. And if he is to be prevented from giving treatment because of the State budget, because of death rates or laws governing immigration, then let them send for the police! (Badiou, 2001)

While most of us can agree, in principle if not in pragmatic terms, to the notion that the benefit of patients should take precedence of bureaucratic considerations like budgets, immigration laws, or statistics that Badiou so contemptuously refers to, Sarah and Peter also ethically challenged me in a way that made Badiou's phrase "everything he knows" ring somewhat hollow. The fact was, I did not know, and nor could I. Sometimes decisions are made on intuition or individual knowledge rather than on the basis of evidence-based medicine. The situation in South Africa asked for a change – something needed to be done to give hundreds of people with HIV and renal failure hope. And transplanting them with HIV-positive organs turned out to be a successful and positive step forward. In the USA, new

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legislation was adopted in 2013 to make it possible to use HIV-positive donors there as well. This was a major step forward for the HIV-positive population in the USA.

6.8 CONCLUSION

For me, the use of HIV-positive donors was something I needed to do to give people hope, but also to address some of the barriers in the medical community in South Africa regarding the disease of HIV. And for these patients, who often had no other options, it was a lifesaving procedure. Starting a research project in a field where there were no clear guidelines, often relying on intuition rather than scientific evidence, was difficult. But the use of high-risk donors in South Africa was a new form of treatment that overcame many medical and social barriers: a risk I feel comfortable with in retrospect today. The complexity of the situation I was presented with included ethical considerations, the historical and social weight of Western medicine in South Africa, badly articulated administrative and managerial structures, scientific consensus favouring evidence-based medicine and the varied kinds of risk associated with tackling this complexity with a combination of clinical experience and expertise, scientific rigor, common sense and empathy for patients that had to bridge the gap between what was knowable and what was not. Progress, I want to suggest, depended in this situation on risks not incompatible with an understanding of clinical decision-making as also complexity-driven, and not only evidence-based. It is this principle that confirms medicine as a domain of research that is not post-human, but humane.

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