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HIV-positive-to-HIV-positive renal transplantation

Chronic kidney disease, predominantly as a result of HIV-associated nephropathy occurs in 20-27% of ART-naïve HIV-infected persons. Of these, a number will go on to develop end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) i.e. dialysis and transplantation.

Until 2008, HIV was a contraindication to RRT. However studies from the US showed that HIV-infected patients transplanted with an HIV-uninfected donor kidney (HIV-negative-to-HIV-positive) had comparable graft and patient survival to uninfected patients. Furthermore, the 1-year results of the first 4 HIV-infected patients to receive an HIV-infected donor kidney (HIV-positive-to-HIV-positive) showed all grafts functioning and no evidence of HIV replication in blood.[1] These transplants were done at Groote Schuur Hospital and were the first in the world. Now, the 3-5 year outcomes of 27 patients undergoing an HIV-positive-to-positive renal transplant has been published.[2] Cumulative patient survival at 1 and 5 years was 84% and 74% respectively, while graft survival was 93% at 1 year and 84% at 5 years. HIV viral load in blood remained undetectable.

Along with these excellent results, come some intriguing questions. Although HIV viral load was undetectable in blood, the chance of low-level incoming viral replication in the transplanted kidney has not been disproved. Indeed, 3 transplanted patients had changes typical of early HIV-associated nephropathy that was not present at baseline. The current low level of primary antiretroviral resistance in South Africa means that incoming virus from the donor is unlikely to be resistant to current regimens. Only 1 out of 15 donors was on NNRTI-based 1st line therapy, the rest were ART-naïve. How such transplants will fare in the future, when resistance may compromise ART control of viral replication is as yet, unclear. Lastly, this work opens the door to the possibility of other types of organ transplantation from HIV-infected donors to HIV-infected recipients.

South Africa, like the rest of the world, continues to suffer from a lack of donor kidneys. This study outlines a way of increasing the donor pool. With such good results, is it any longer ethical to withhold the possibility of an HIV-infected kidney to an HIV uninfected patient (HIV-positive-to-HIV-negative) should the possibility arise? In other words, should HIV-infected donors just be added to the general donor pool? An HIV-infected patient now has the option of receiving either an HIV-infected kidney or one from an HIV-uninfected donor. The same is not true for HIV-uninfected patients with ESRD requiring RRT, who only have the option of an HIV-uninfected donor. In a health system that sees many patients with ESRD sent home to die because of a lack of RRT options, if you were given the choice, would you take an HIV-infected kidney? ART started simultaneously should prevent HIV-associated morbidity & mortality.

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Pre-exposure prophylaxis (PrEP): recent findings add to the evidence that it is effective as an HIV prevention tool

Oral pre-exposure prophylaxis (PrEP) refers to an HIV-seronegative person who is at risk of HIV infection taking antiretroviral drugs to prevent HIV acquisition, either continuously or timed around potential exposures. To date PrEP has been shown to be effective in reducing HIV acquisition in some studies, but not in others. This variation in findings appears to be related to adherence: where PrEP is taken with good adherence it appears to work.[1]

Two large randomised controlled trials of PrEP in men who have sex with men (MSM) were presented at this year's CROI in Seattle: the PROUD and IPERGAY studies.

The PROUD study[2] was conducted among 545 MSM identified to have high risk behaviours attending sexual health clinics in London. Participants were randomised to commence daily tenofovir/emtricitabine (TDF/FTC) PrEP immediately (n=276) or to defer for one year (n=269). There were 3 incident HIV infections in the immediate arm (annual incidence of 1.3%) and 19 in the deferred arm (annual incidence of 8.9%). This meant that being prescribed PrEP reduced HIV incidence by 86% (90% confidence interval = 62-96%).

The IPERGAY study[3] conducted in France and Canada involved 400 MSM participants who were at high risk for HIV infection. It was a randomised controlled trial comparing TDF/FTC versus placebo. Participants were asked to take 2 tablets from 1 day to 2 hours before they anticipated having sex, a 3rd pill 24 hours after sex and a 4th pill 48 hours after sex. If they had further sexual activity during this period they were instructed to continue taking TDF/FTC daily until 48 hours after their last sexual encounter. Two participants in the TDF/FTC arm seroconverted and 14 in the placebo arm, meaning an 86% reduction in HIV incidence (95% confidence interval =39-99%). Interestingly the relative reduction in new HIV infections associated with PrEP prescription in both studies was exactly the same (86%). TDF/FTC PrEP was well tolerated in the majority of participants with very few cases of renal abnormalities, mainly transient, occurring on drug in the two studies.

The SA HIV Clinicians Society has published PrEP guidelines for MSM.[4] HIV testing, hepatitis B screening and calculation of creatinine clearance should be done in all individuals before starting PrEP. Creatinine and HIV status should be monitored in patients on PrEP.

The prescription of PrEP should be discussed with HIV-seronegative patients who are at high risk for HIV acquisition. There is good evidence for its efficacy in those MSM who based on sexual history are identified to be at high risk of HIV infection. Another group that could be considered is commercial sex workers. There is also evidence that PrEP is protective for the HIV-seronegative partner in a serodiscordant couple[5] and this should be particularly considered when the HIV-infected partner is not on ART or during the first 6 months that the HIV-infected partner is taking ART before the HIV viral load is suppressed. Because PrEP efficacy appears to be very dependent on adherence, PrEP should only be prescribed in those individuals who are motivated to take the PrEP and have the appropriate follow-up for monitoring. It should be provided as part of a package of HIV prevention interventions including risk reduction counselling and condoms.

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Use of raltegravir in children

Introduction
Raltegravir, an integrase inhibitor, is registered in South Africa and recently more child-friendly formulations have become available. These are suitable for infants (4 weeks of age and a weight ≥ 3 kg), children and adolescents.[1]

The pharmacology of Raltegravir
The major route of raltegravir elimination is glucuronidation by uridine diphosphate glucotransferase (UGT). Of note is that this enzyme is responsible for bilirubin metabolism and has lower activity in newborns. Bilirubin and raltegravir compete for both UGT and albumin binding sites, therefore neonatal hyperbilirubinaemia can be exacerbated.[2]

The basis for current dosing and usage
Most pharmacokinetic data for raltegravir in children was obtained from the IMPAACT P1066 study. This Phase I/II study assessed the pharmacokinetic (PK) profile, safety and tolerability of child-friendly formulations. Only antiretroviral-experienced children were studied.

Infants > 4 weeks of age and toddlers up to the age of 2 years could enroll if they had been exposed to antiretroviral drugs either through prevention of mother to child transmission or a failed therapeutic regimen. Twenty-three children completed the 48 week study with 44% being suppressed at study end. Children 2 - 18 years could enroll if they had experienced virological failure. Ninety-one children and adolescents completed 48 weeks of therapy with 57% achieving suppression. Poor adherence and new resistance were the main reasons for failure. It is important to note that all children in the IMPAACT P1066 study were exposed to antiretrovirals prior to enrolment and that the majority received a boosted protease inhibitor (darunavir) with optimized background therapy.[3]

There is no dosing data for raltegravir in neonates although this is being studied.

There is no published cohort data for raltegravir in first line therapy in children. Experience with raltegravir as part of an optimized regimen is growing with good results being reported both locally and internationally in salvage regimens.[4]

For children with tuberculosis, there is an ongoing study to determine appropriate dosing of raltegravir in children requiring rifampicin. Currently there are no dosing recommendations for this situation. UGT is induced by rifampicin and concentrations of raltegravir are reduced. Doubling the dose was suggested to overcome the drug interaction, but a small randomised controlled trial in adults on rifampicin-based TB therapy showed that standard doses of raltegravir were as effective as double doses.[5]

Some points to note
Raltegravir is available as granules, 25 mg and 100 mg chewable tablets and 400 mg film-coated tablets. These formulations **are not interchangeable** and not bioequivalent. Dosing is according to weight band and formulation specific (see table below).

Raltegravir dose from 4 weeks to 12 years (± 6 mg/kg)

Weight (kg)	Dose of Suspension to be administered	Chewable tablets (25mg and 100mg)	Film-coated tablet (400mg)
3 to < 4	20mg twice daily		
4 to < 6	30mg twice daily		
6 to < 8	40mg twice daily		
8 to < 11	60mg twice daily		
11 to < 14	80mg twice daily	75mg (3 x 25mg) twice a day	
14 to < 20	100mg twice daily	100mg (1 x 100mg) twice daily	
20 to 25		150mg (1.5 x 100mg) twice daily	
25 to 28		150mg (1.5 x 100mg) twice daily	400mg (1 x 400mg) twice daily
28 to < 40		200mg (2 x 100mg) twice daily	400mg (1 x 400mg) twice daily
≥ 40		300mg (3 x 100mg) twice daily	400mg (1 x 400mg) twice daily

Most children tolerate raltegravir but serious toxicity can occur. Common problems include nausea, headache, dizziness, diarrhoea, fatigue, itching and insomnia. Abdominal pain and vomiting as well as hepatitis with or without jaundice can occur. In adults hepatitis is more common in patients co-infected with hepatitis B or C. Rare but serious adverse reactions include severe drug rash, Stevens Johnson syndrome and toxic epidermal necrolysis, thrombocytopenia, myopathy and rhabdomyolysis.[2]

Although adults can now take raltegravir as part of first line therapy in certain circumstances, most South African children receiving raltegravir are on a third-line regimen that includes boosted darunavir. Approval for the use of raltegravir as third line therapy in the state sector is only given to children with confirmed protease inhibitor resistance and with at least partial resistance to darunavir. Although using raltegravir as first line therapy or if intolerant to another agent is not common, it can be considered after discussion with an experienced clinician. As with other antiretroviral therapies raltegravir should not be added as a single drug to a failing regimen.

Raltegravir has a low resistance barrier, it should be discontinued in children who do not suppress viral replication, as continued use may compromise newer integrase inhibitors such as dolutegravir. Where integrase inhibitor resistance is suspected and a resistance test is requested, raltegravir usage should be noted in the request form to ensure that the integrase enzyme is sequenced.

Conclusion

The availability of raltegravir in child-friendly and tolerable formulations adds a potent drug in a "new" class for children. With darunavir, it is the backbone for children requiring third line therapies. In the future raltegravir may play an important role in maternal therapy during pregnancy and in prevention programs.

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Balancing risks and benefits in post exposure prophylaxis

People with HIV infection have a near-normal lifespan provided that antiretroviral therapy is not started too late, so the risks of post exposure prophylaxis (PEP) need to be more carefully considered than in the past. On the other hand, newer antiretroviral drugs are considerably safer than most of the older agents. Most international guidelines on PEP, including the recently published World Health Organization guidelines,[1] recommend three antiretroviral drugs for both low- and high-risk exposures. There are no controlled data on the efficacy of any PEP regimen. There is also limited controlled data on the safety of antiretroviral drugs in HIV-uninfected people, except for tenofovir plus emtricitabine from pre-exposure prophylaxis trials. It cannot be assumed that antiretroviral safety will be similar in HIV-infected and HIV-uninfected people, as illustrated by the severe toxicity of nevirapine when used in PEP. Therefore it is not possible to accurately determine risk:benefit ratios for PEP.

Without PEP the risk of HIV after percutaneous exposure to HIV-infected blood (needlestick injuries, which are high risk exposures) is 0.3%, and is reduced by 81% with zidovudine monotherapy,[2] which translates into a number needed to treat to prevent one HIV infection of 412. It is assumed that the addition of extra antiretroviral drugs will be more effective, but anecdotal cases of PEP failure indicate that efficacy is not 100%. The number needed to treat to prevent one HIV infection with three drug PEP would be 350 if efficacy were 95%. With low risk exposures (e.g. the risk of acquiring HIV from unprotected vaginal intercourse with an HIV-infected woman is 0.05%) the number needed to treat is unknown but is likely to be about an order of magnitude higher than with needlestick injuries.

Life-threatening adverse drug reactions from currently recommended antiretroviral drugs are uncommon, likely occurring in about 1 in 1,000 people, except for emtricitabine and lamivudine, which are considerably safer. People on the month long course of PEP are at risk of life-threatening reactions as many of them occur early (e.g. acute renal failure from tenofovir and severe hypersensitivity reactions). Therefore the number needed to harm (with life-threatening adverse drug reactions) may be similar to or lower than the number needed to treat to prevent one HIV infection when three drug PEP is used following low-risk exposures.

In the absence of definitive data clinical judgement needs to be used when balancing risks and benefits for PEP. It is reasonable to start three drug PEP following an HIV exposure event. However, clinicians should have a low threshold to switch or stop offending antiretroviral drugs should potentially severe adverse drug reactions occur. There is still a place for two drug PEP for very low risk exposures.

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