Short-term outcomes of down-referral in provision of paediatric antiretroviral therapy at Red Cross War Memorial Children's Hospital, Cape Town

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DECLARATION

I, *Julie Copelyn*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background: The large scale-up of paediatric HIV care necessitated down-referral of many children receiving antiretroviral therapy (ART) from Red Cross War Memorial Children's Hospital (RCWMCH). No published data exists on the outcomes of these children.

Objectives: To assess clinical, immunological and virological outcomes of children receiving ART in the first 12 months after down-referral to primary health care (PHC) clinics, and identify determinants of successful down-referral.

Methods: We conducted a retrospective cohort study of children <15 years of age who commenced ART at RCWMCH and were subsequently down-referred to one of two PHC clinics between January 2006 and December 2012. Baseline characteristics of patients and caregivers as well as CD4 counts, viral loads and weights were collected at 6 and 12 months post-down-referral. Outcomes included retention in care and viral suppression.

Results: One hundred and sixteen children down-referred to Heideveld and Gugulethu were included. After down-referral 13.8% of the cohort never arrived at the designated clinic and 10% took longer than 8 weeks, therefore probably experiencing treatment interruption. At 12 months post down-referral only 68.2% remained in care at the designated clinics. No factors were associated with retention in care. For those children who remained in care at the PHC clinics, the clinical and immunological gains achieved prior to down-referral were sustained through 12 months of follow up, and 54.7% of the retained cohort had documented viral suppression at 12 months.

Conclusion: Down-referral of children on ART is a vulnerable process with risk of loss to follow-up and treatment interruption.

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Lists of tables & abbreviations

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Abbreviations:

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
CHBH	Chris Hani Baragwanath Hospital
CTCs	Care and treatment centres
HAZ	Height-for-age *z*-score
HIV	Human Immunodeficiency Virus
LTFU	Loss to follow up
PHC	Primary health care
PHF	Primary health facility
PMTCT	Prevention of mother-to-child transmission
RCWMCH	Red Cross War Memorial Children's Hospital
SHF	Secondary health facility
VLs	Viral loads
WAZ	Weight-for-age *z*-score
WHZ	Weight-for-height *z*-score
WHO	World Health Organization

Chapter 1: Literature review

Background

The HIV/AIDS epidemic has had a dramatic impact on the health of South Africa's children, contributing substantial morbidity and mortality. Without antiretroviral therapy (ART) more than 50% of perinatally infected children will die before their second birthday[1]. The South African national ART programme was launched in April 2004, and is now the biggest programme in the world with over 3 million people receiving ART[2]. Although paediatric coverage has increased from just over 9% in 2004/2005[3] to 63% by the end of 2012, the treatment gap favouring adults has persisted in South Africa, as in many other low- and middle-income countries[4]. Paediatric treatment programmes suffered from many of the same barriers to improving ART coverage as adult programmes, including human resource and health facility limitations – which were more pronounced in rural areas. In the push for a rapid scale-up of ART provision and improvement in ART coverage, the South African government adopted the 'public health' approach to HIV care that the WHO had been promoting since 2001[5]. Central to this approach are the two closely linked concepts of task shifting and decentralization. Task shifting entails 'lower' cadres of health care providers, and sometimes non-professionals, taking over responsibilities previously held by doctors or 'higher' cadres of health care workers[6]. Decentralizing care is the process of moving care from tertiary referral centres to health care centres, clinics, and even beyond clinics into communities - closer to patient's places of residence[7]. For many patients, particularly those already receiving care from tertiary hospitals this has required a process of 'down-referral' to treatment sites with less specialized health care facilities.

By 2007/2008 the Western Cape paediatric ART coverage rate had improved to over 95%, well exceeding the national average of 37%[8]. This was a consequence of both significant gains in preventing mother-to-child-transmission of HIV as well as expansion of the paediatric HIV programme into primary health care (PHC) settings. This decentralized model of care necessitated the down-referral of large numbers of children from tertiary academic hospitals to community-based clinics. To date there is very little data on the outcomes of down-referred children worldwide, and the cohort

from Red Cross War Memorial Children's Hospital (RCWMCH) specifically, has never been studied.

Objective

The objective of this literature review is to assess the impact of decentralizing paediatric ART provision by down-referral of patients from tertiary centres to PHC clinics.

Search strategy

The issues around scale-up of ART provision, and down-referral of patients are relatively new, thus published data and research are limited. A broad search was therefore conducted on a number of database platforms:

- Pubmed
- Ebscohost
- Web of Science
- The Cochrane database.

The abstract archive of the International Aids Society (http://www.abstract-archive.org/) was also searched for relevant unpublished research.

Search terms used included MeSh terms and free text:

- HIV, Child, Paediatric/ pediatric, decentralization, "down-referral" and "transfer out."

The bibliographies of relevant articles were also searched for additional papers.
The search was originally done in June 2012 and then repeated in January 2016 prior to submission.

Acceptable studies/ inclusion criteria

As the evidence is so limited inclusion criteria were deliberately left broad:

> ***Population***: Adults and children
> ***Intervention***: A process of down-referral or decentralization of HIV care
> ***Comparator***: Retention in care at site of initiation
> ***Outcome***: All treatment outcomes (loss to follow up, death, virological suppression)

Results

Despite the broad search strategy and inclusion criteria, data were limited.
From the Cochrane database there was one systematic review of decentralized care, looking at outcomes in both adults and children. There were 7 further studies looking at outcomes in decentralized models of HIV care in adults and children, and only 2 studies that looked exclusively at outcomes of down-referred paediatric patients.

A further 12 articles were included in this review as they relate broadly to the topic of the decentralization of HIV care and ART provision.

Discussion

Down-referral is a small component of the larger policy of creating a decentralized model of care for HIV-infected patients. Before being able to assess the impact of the down-referral process, one first needs to ascertain whether patient outcomes at the various different levels of care are comparable.

Outcomes at different levels of care – adult data

Evidence from the adult literature suggests that treatment outcomes at primary health care clinics are at least as good if not better than at tertiary hospitals. In a retrospective cohort study of over 29 000 ART naive adults who commenced ART at one of 59 treatment centres in South Africa, Fatti et al. report superior outcomes at PHC facilities[9]. Despite having more advanced clinical stage of disease at the time of initiation, no significant differences in mortality rates after 24 months of treatment could be found between patients at PHC clinics and those managed at secondary and tertiary hospitals[9]. Furthermore, patients managed at PHC clinics had less loss to follow up (LTFU) at 24 months of treatment (8.9% vs. 17.9%), and greater retention in care (80.1% vs. 68%) than patients managed at secondary and tertiary hospitals. A similar sized study assessing decentralization of HIV care in Kenya, also found no difference in mortality rates between patients managed at primary or secondary health facilities[10]. In contrast to the South African study, this study found no significant difference in rates of LTFU of patients on ART. Both studies, thus providing evidence of equitable outcomes for HIV-infected adults managed at different levels of health care.

There are a number of unique issues in the management of HIV-infected children that make it impossible to generalise from the adult data. Rates of adherence and loss to follow up are governed by a child's caregiver – on whom they are entirely dependent. In this context, caregivers are often HIV-infected themselves with varying degrees of health, or they are elderly family members caring for an orphaned child. Another obstacle is the large number of medications, some unpalatable, that the child is required to take[11]. These differences between adult and paediatric care make it imperative to assess paediatric outcomes independently.

Outcomes at different levels of care – paediatric data

There are two studies that have compared treatment outcomes of children on ART between different levels of care. In a 2007 study, Bock et al. conducted a retrospective review of routinely collected data from a cohort of children in the Western Cape who had initiated ART between April 2004 and April 2006[12]. Of the 1741 children, 20.7% were managed at primary health care (PHC) level, 13.6% at district hospital level, and 65.7% at level 2 & 3 hospitals. Overall 46% of the cohort commenced ART with severe immunodeficiency with CD4 counts < 15%. Survival estimates at 12 months after commencing ART were 0.88 (95% CI: 0.86 – 0.9) at level 2 &3 hospitals, and 0.94 (95% CI: 0.89-0.97) and 0.94 (95% CI: 0.89 – 0.9) at both PHC and district hospitals respectively. Rates of death at 12 months were 13.2% (95% CI: 10.3- 16.5) and 2.6% (95% CI: 0.5 – 6.9) at level 2 & 3 hospitals and PHC clinics respectively. The percentage of children with suppressed viral loads (defined as <400 copies/ml) after 12 months of treatment with combination ART was 70.5% (95% CI: 64.9 – 75.9) at level 2 &3 hospitals, and 81.4% (95% CI: 72.4 – 88.4) at PHC clinics. This data suggests that children receiving combined ART from PHC clinics do no worse – and possibly better than children at secondary and tertiary hospitals.

Fayorsey et al.[13] reached similar conclusions in their study of 8475 children from 5 sub-Saharan African countries. They retrospectively reviewed routinely collected programmatic data from 274 health facilities in Kenya, Rwanda, Tanzania, Lesotho and Mozambique. Between January 2008 and March 2010, 17155 children under the age of 15 enrolled in HIV care, 8475 of whom were initiated on ART. During the study period, the majority (71%) of children who were initiated on ART, did so at secondary/ tertiary health facilities (SHFs) rather than at primary health facilities (PHFs). There was, however, a significant trend towards decentralizing paediatric HIV care over the two year period. The number of PHFs providing HIV care to children increased threefold, from 56 to 182, in comparison to an increase of SHFs from 72 to 92. This accounts for a 22.6% increase in the contribution of PHFs to the total number of centres providing paediatric HIV care. As the number of PHFs increased, so to did the contribution they made to initiating and maintaining children on ART. Every quarter an increasing number of children were initiated on ART at PHFs – an increase of 2.8 times over the 2 years of the study. Rates of mortality and LTFU were reported as 5.2/100 person-years (PY) vs 6/100 PY (p=0.001) and

9.8/100 PY vs 20.2/100 PY (p=0.003) at PHFs and SHFs respectively. This study, while not addressing the issue of 'transfer-out', does provide further support for the process of decentralizing paediatric HIV care, with evidence of superior outcomes at PHFs.

Down-referral of patients on ART – adult data

As the decentralization of HIV care gained momentum a number of studies started to look specifically at the outcomes of patients who were 'transferred-out' or 'down-referred' from one health care facility to lower levels of care. Three South African studies reported positive outcomes for down-referral of adults on ART. O'Connor et al. reported extremely high rates of retention in care from a cohort of 3361 patients in an inner city Johannesburg treatment service[14]. Patients became eligible for down-referral to one of four nurse-managed PHC clinics once they were clinically stable, with improving CD4 counts and undetectable viral loads, good adherence and on ART for at least 6 months (mean 1.56 years). Patients who missed their scheduled appointments by more than 6 weeks were aggressively traced, initially telephonically, and then by home based care workers. During the study period only 4.1% of patients were LTFU, 95.5% were retained in care (of whom, 3% were receiving care outside of the down-referral programme) and less than 1% of patients retained in care had been transferred back to the treatment initiation site. Unfortunately this paper provides no information about the duration of follow up after down-referral, and this would likely introduce bias in favour of down-referral if the follow up time at PHC facilities was low. Importantly however, of those patients who were lost to follow up, 58% never arrived at the down-referral site – hinting at the vulnerability of this process of transferring patients between treatment sites. Finally, this study did not evaluate clinical, immunological or virological outcomes after down-referral. Despite good retention in care it is thus impossible to comment on the quality of the care provided.

Comparably high rates of retention in care were reported from another inner city Johannesburg treatment site after down-referral from a doctor-managed HIV clinic to a nurse-managed PHC clinic. In this setting, patients became eligible for down-referral only after 11 months of ART, with evidence of good adherence (2 suppressed viral loads, CD4 > 200 cells/μl) and clinical stability (<5% weight loss over last 3

visits and no opportunistic infections)[15]. Of the patients who met down-referral criteria, less than 35% were actually transferred out. Some patients were not offered down-referral and others refused, both for undocumented reasons. This low rate of uptake of down-referral has the potential to bias outcomes in favour of the down-referral model. The two sites in this study (the 'treatment initiation' site and the down-referral site) were closely integrated through an electronic patient management system. This allowed for easy transfer of patient medical records between the sites, as well as system alerts to remind the provider when patients were eligible for down-referral or required referral back to the treatment initiation site[15]. In a matched-cohort analysis of those patients who were down-referred and those who were retained at the treatment initiation site, better outcomes were reported at the nurse-managed down-referral clinic. Twelve months after down-referral eligibility, loss to follow up was 1.4% vs. 4.2%, mortality rates were 0.3% vs. 1.5% and rates of virological rebound were 3.3% vs. 5.6% in the down-referred and non down-referred groups respectively. In the same treatment setting, Long et al. focused on the cost saving benefits of down-referral[16]. They report a financial saving of 11% per patient per year. This saving persists despite 17% of transferred patients having been transferred back to the treatment initiation site within an average of 6.1 months post down-referral.

One South African study reported higher rates of LTFU in patients down-referred from a doctor-managed ART clinic to a nurse-managed programme in a peri-urban community health center in Gugulethu, Cape Town[17]. Down-referral criteria in this study included at least 16 weeks of first line ART therapy, a recent viral load <50 copies/ml, no opportunistic infections or poorly controlled chronic illnesses, and documented adherence based on pill counts. Data were collected prospectively on 5746 patients, and the primary outcomes measured included death, LTFU and virological failure[17]. The study found no significant differences in either mortality [aHR 1.51 (95% CI: 0.9 – 2.55)] or virological failure [aHR 0.94 (95% CI: 0.78 – 1.13)] between the down-referred and non down-referred groups. In contrast to the other three South African studies cited above however, rates of LTFU in this study were found to be higher in the down-referred group than those retained at the doctor-managed clinic [aHR 1.36 (95% CI: 1.09 – 1.69)]. Down-referred patients had fewer scheduled clinic appointments, with ART being dispensed at the pharmacy for 2 months at a time, and clinical follow ups with nursing staff scheduled every 4 months

only[17]. This reduced the opportunities for adherence support and individualized counseling. Furthermore, an important difference in this study is that the treatment initiation site and the down-referral clinic were both located on the same physical grounds at the Gugulethu CHC. This would diminish the positive effect of the advantages of down-referral such as accessibility and reduced travel times. Furthermore it becomes unclear whether the measured effect is secondary to down-referral or task- shifting.

A final study that looked at the effects of decentralizing access to antiretroviral therapy for adults was conducted in Swaziland. This study compared rates of LTFU and death amongst patients whose ART was either partially or fully decentralized with those whose care was maintained at central treatment initiation sites (hubs)[18]. Partial decentralization was defined as patients who initiated ART at hubs and were subsequently down-referred to PHC clinics (spokes). Full decentralization of care was achieved if ART was initiated at spokes. In both models of care ART initiation was done by doctors, and ongoing care at PHC clinics was provided by nurses. The overall rates of death and LTFU at 1 year after ART initiation in this study were 3% and 16% respectively. Down-referral was strongly protective against LTFU [aHR 0.38 (95% CI: 0.29 – 0.50)] but not mortality.

Down-referral of patients on ART - studies combining adult and paediatric data

Further evidence in favour of down-referral of HIV care comes from two studies from Malawi. Importantly, both of these studies included both adults and children in their analyses. As in South Africa, the large scale-up of ART provision in Malawi was hindered by both financial and human resource constraints. Furthermore the centralization of care was thought to contribute to the suboptimal reported rates of retention in care, and to increase inequality in health care provision for poor rural communities[19]. Consequently the process of decentralization of ART provision began. In a retrospective review of 4175 patients (10% of whom were children) commencing ART over a three year period in Mzuzu Central Hospital in Northern Malawi, 19% were found to have been transferred out[20]. Of the transferred out cohort – 92% were traced, and of these patients, 90% were found to have transferred in to a new treatment centre. The median time between transfer out and transfer in was just over 1 month, suggesting that patients were unlikely to experience treatment interruptions as

a result of the transfer process[20]. In this study there was no significant difference between rates of loss to follow up between those transferred out and those retained in centralized care, however those transferred out had significantly lower mortality rates [OR 0.4 (95% CI: 0.3 – 0.6)].

In the mostly rural Zomba district in Southern Malawi, decentralization of HIV care was achieved through incorporation into routine outpatient services at rural health centres[19]. In a retrospective review of 8093 patients who commenced ART over a 4 year period, 4653 were retained at the central hospital site, and 3440 were 'decentralized' to health centres, this included 1005 (29%) patients who were managed solely at the decentralized site (i.e. not down-referred.) In this cohort of patients, decentralization of care was associated with lower rates of mortality [OR 0.19 (95% CI: 0.15 – 0.25)] and defaulting from care [OR 0.28 (95% CI: 0.4 – 0.58)][19]. Although the data from this second study includes both patients who were down-referred as well as some who exclusively managed at peripheral health centres, it still lends further support to the model of decentralization and down-referral of HIV care.

Down-referral of patients on ART - paediatric data

Only two studies have looked exclusively at the outcomes of down-referral of children receiving ART. Despite significant differences in the setting and the design of these studies – both reported good clinical and virological outcomes. In a Thai study, the outcomes of 168 children who were down-referred from a centralized tertiary hospital to 1 of 16 'community hospitals' were reviewed. Community hospitals had at least 2 healthcare professionals, including doctors, nurses and pharmacists as well as people living with HIV, who did home visits and adherence counseling[21]. After down-referral, close relations were maintained between the tertiary and community hospitals – with teleconferences and individual case reviews. Furthermore, children returned to the tertiary centre for review by a paediatrician every 6 months[21]. Down-referral criteria in this cohort included being clinically stable, with no opportunistic infection, improving weight and CD4 counts, as well as having a willing caregiver. Interestingly, as this study was conducted shortly after the implementation of the Thai national ART programme, the participants tended to be older and more severely immunocompromised (median age 8.6 years, and 39% of

entire cohort had a CD4 count of less than 5% at initiation[21]). Despite this, the rates of retention in care and adherence are impressive. Of the 168 children down referred to community hospitals, with a median follow up time of 18 months, only 6 children (3.5%) were referred back to the tertiary hospital for continuation of care and no children were lost to follow up[21]. Adherence in the entire cohort was >95% (measured on pill counts or volume measurements) over 48 months of follow up, with no significant difference between the down-referred or the retained in care groups. During the study period 10% of the cohort died, representing a crude mortality rate of 4.1/100 PY of follow up (95% CI: 3 – 5.6). Of these deaths, 60% were reported in the first 90 days of treatment, and none of the deaths were in the down-referred group[21]. This reflects both the stability of the patients chosen for down-referral and the length of time on treatment before down-referral. When the programme started, time to down-referral was 31 months, but for children who started ART after September 2006 the time had reduced to 8 months.

Clinical and virological outcomes were comparable between the 2 groups. Children from the down-referred group initiated ART from a lower weight-for-age *z*-score (WAZ) baseline than those retained in care (median WAZ -2.1 vs. -1.6, p = 0.001). There was however, no difference in the rate of weight gain between the two groups. The median CD4% increased from 6% at baseline to 26% at 48 months of follow up, and the number of children with a CD4% below 15% declined from 80% to 4.8% in the same time frame. Again there was no significant difference between the two groups. The number of children with serial viral loads available was limited, however of those available, >86% of children who were ART naïve at initiation had undetectable viral loads (less than 400 copies/ml) at 48 months of follow up. This study has shown that with high levels of support – both within the community for patients and their caregivers, as well as at the down-referral sites for the treating health professionals, that highly successful outcomes for a decentralized model of paediatric HIV care are possible. The older age of the cohort, the small numbers treated at each community hospital, as well as the intensive adherence monitoring and counseling makes it unclear if the results of this study could be generalized to a South African context.

In 2014 Morsheimer et al. published their findings of a cohort of down-referred children in the Western Cape, South Africa[22]. This study differs from the Thai study, as well as from many of the adult studies, in that down-referred patients were identified at the PHC clinic rather than at the site of ART initiation, and then compared to patients who were initiated at the same PHC clinic. Thus the outcomes of any patients who were lost during transfer were not captured. The study was done at a time when the decentralization of paediatric HIV care was gaining momentum. Between March 2004 and September 2006 the percentage of children receiving their ART from the three Cape Town tertiary hospitals declined from 78% to 38%, and the number of clinics treating children with ART increased from 11 to 41[23].

In this context, Morsheimer et al. conducted a retrospective review of 613 children who were either down referred for continuation of ART or initiated on ART at 1 of the 7 community-based paediatric ART clinics supported by the paediatric infectious diseases team from Tygerberg Children's Hospital. The median age of the children in this study was 26.4 months (IQR 10.2 – 63), substantially lower than the children in the Thai study. Of the 613 children included in this cohort, 343 were initiated at the PHC clinics, and the remaining 270 had been down-referred from tertiary hospitals. For the down-referred group the median follow up time was 28 months. During that time only 1 patient required transfer back to the tertiary care site, and 1 patient died (0.6%)[22]. The down-referred patients were significantly sicker at initiation than those who initiated treatment at PHC level; 89.8% of them vs. 70.7% of PHC initiates had WHO stage III/IV at initiation ($p< 0.0001$), they also had higher baseline viral loads (median: 326 969 vs. 230 000 copies/ml, $p = 0.0004$) and increased rates of concomitant TB infection at initiation (25.3% vs. 16.9%, $p = 0.013$)[22]. It also took longer (44 vs. 29 weeks) for those who were down-referred to achieve viral suppression (<400 copies/ml). Importantly however, of the 80% of patients who were down-referred with suppressed viral loads, 96% showed sustained viral suppression at last study evaluation[22]. Twenty-six patients were down-referred with unsuppressed viral loads, many of whom met criteria for virological failure, and most of whom had documented concerns of poor adherence. After 6 months of treatment at the PHC site, 77% of these children were able to achieve virological suppression on first line ART, avoiding the need to change to second line ART. This is important for a number of reasons; firstly it is unique in the literature to have patients down-referred with

unsuppressed viral loads, as most centres have used viral suppression as a criterion for down-referral. Secondly, it challenges the notion that higher levels of care will have more success in achieving the desired virological outcomes. Most importantly however, it suggests that for those patients where adherence is an issue, outcomes may in fact be better at treatment centres closer to home, possibly by reducing the barriers to accessing care[22]. As with the Thai study, this study has shown good treatment outcomes for children down-referred to PHC clinics for continuation of their ART.

Decentralized care: systematic review

In 2013 Kredo et al. published the first (and to date only) Cochrane review of decentralization of HIV care in lower- and middle-income countries[7]. In this review they described three patterns of decentralization: 'full decentralization' which entails initiation and maintenance of ART at peripheral sites, 'partial decentralization'- commencing ART at central hospitals and then down-referring patients to peripheral sites for ongoing care, and 'community based models' where ART is commenced in a health centre or hospital but is continued in the home environment with support provided by health care workers or volunteers[7]. Sixteen Studies were included in this review, 1 from Thailand the other 15 from African countries. The strongest evidence was in favour of 'partial decentralization' or down-referral. At 12 months of follow up, in comparison to remaining in centralized care, the risks of attrition, LTFU and death in the down-referred group were RR 0.46 (95% CI 0.29 – 0.71), RR 0.55 (95% CI 0.45 – 0.69) and 0.34 (95% CI 0.13 – 0.87) respectively. This review included studies of both adult and paediatric patients, including many of those discussed above.

Concerns regarding decentralized care

The literature thus seems conclusive as to the positive benefits of decentralization and down-referral in both adult and paediatric populations. There are however, a number of studies that highlight significant areas of concern. In 2008 Mukora et al. conducted 10 focus group discussions with 76 patients receiving ART at Chris Hani Baragwanath hospital (CHBH)[24]. Their aim was to assess patient attitudes to down-referral of their HIV care from the central CHBH to peripheral PHC clinics in Soweto. In these focus group discussions patients acknowledged the advantages of down-referral, specifically closer proximity to home with the resultant reduction in

transport costs and time at clinic. Despite this, 63% of the participants were opposed to down-referral. They cited concerns of increased stigma and reduced confidentiality at peripheral PHC clinics, as well as a preference for continuing doctor led care. Furthermore, they expressed uncertainty about the quality of care at the PHC clinics and perceived negative nursing attitudes and lack of nurse training in HIV management[24]. Importantly, the patients in this study had no experience of down-referral as the study took place prior to the implementation of decentralized care.

A more concerning study was published in 2014 by Ostermann et al.[25], which evaluated the effect of the rapid scale-up of decentralized HIV care in Northern Tanzania. In this prospective cohort study, there was a concerning trend for patients to bypass many closer care and treatment centres (CTC's) in favour of established facilities. Despite a large increase in the number of CTC's in the study area, after 3.5 year of follow up, only 2% of patients who had been initiated at the referral hospitals had been transferred-out, and almost 75% of patients newly enrolling in HIV care did so at the referral hospitals[25]. Compounding these concerns is a study from rural South Africa, which, despite acknowledging the positive outcomes of down-referral, highlighted the potential unseen additional health care expenses incurred by down-referred patients[26]. In this study, down-referred patients were 7 times more likely to have visited private physicians and 5 times more likely to have engaged in 'self-care practices' than those retained in care. In 27% vs. 11% of the down-referred and retained in care patients respectively, this represented a 'catastrophic healthcare expenditure'. This increased use of private doctors may be the result of the expressed patient preference to be seen by doctors. Regardless of the reason, the increased financial burden incurred in the down-referred group raises concerns over sustainability and long-term retention in care.

In a case report study of decentralization of HIV care in Tete city in Mozambique, Decroo et al. describe the programmatic consequences of a poorly planned down-referral process[27]. In this report, 30% of down-referred patients were lost to follow up. This was thought to be secondary to the rapid rate of decentralization and inappropriate planning. As a large number of patients were transferred to PHC clinics in a short period of time, the capacity and human resources of these clinics were rapidly overwhelmed, resulting in long waiting times and unreliable drug supplies[27].

Unfortunately it is not clear from this report at what stage in the transfer process patients were lost to follow up. In a study from central Johannesburg, although the overall LTFU rate was only 4.1% almost 60% of these patients were lost at the point of transfer out and never presented to the PHC at all[14]. This suggests that there is an intrinsic vulnerability to the process of transferring patients from one treatment site to another, and that in order to reduce LTFU, special attention needs to be given to managing this event.

Although there is now a growing body of research and data looking at the issues of decentralization, task shifting and down-referral, many concerns and questions still remain. In most of the published studies, down-referral was highly selective, not only were the patients clinically stable, but they were agreeable to down-referral – this could obviously introduce bias in favour of down-referral. Secondly, whilst some studies have reported very low rates of transfer back to higher levels of care, some have reported rates of up to 17%[16]. The outcomes of patients who are reluctant to be down-referred is still unclear, and in this context the 30% LTFU reported by Decroo et al.[27] is concerning. Furthermore, in a number of the studies that report very good treatment outcomes post down-referral, the level of interaction and integration between the central hospital and the down-referral sites far exceeds that available in other resource poor settings. In some studies this is by way of physical proximity, electronic patient management systems or regular contact and case discussions between care providers in the different settings[15,21]. In the two published paediatric studies, although there was definite decentralization and down-referral, there was less task shifting. In the Thai study[21], patient management was still ultimately controlled by the specialist in the referral hospital, and in the South African study[22], patients in the PHC were seen by specialist doctors trained in paediatric HIV care. Finally, although clinical and virological stability have been used as prerequisites in most studies – there is some evidence of benefit in down-referring those patients with adherence issues, thus the question of down-referral criteria and optimal timing of down-referral still need to be answered.

Down-referral is a central component of the package of care provided by the RCWMCH paediatric HIV programme. To date, no assessment has been made of the impact of this intervention nor has any review of the outcomes of these children been

attempted. As illustrated above, the available evidence from paediatric data is severely limited, and conclusions are not necessarily generalizable to this cohort of patients. RCWMCH down-refers large numbers of patients for ongoing HIV care. It is imperative that we try to understand the effect that this transition has on our patients, and whether they are, in fact, able to safely navigate the down-referral process without ill effect.

Table 1: Summary of Literature

Study	Setting	Design	Study population	Outcomes
Outcomes at different levels of care:				
Adults				
Fatti G et al.[9] (2010)	South Africa	• Retrospective cohort • Multi-centre • Comparing outcomes at PHC facilities, district and regional hospitals	29 203 adults ART naïve	Better outcomes at PHC: • Retention in care at 2 years: 80% at PHC, 68% at regional hospital • LTFU increased at regional hospitals at 1 year: aHR 2.19 (95% CI: 1.94 – 2.42) • Mortality increased at district hospitals at 1 year: aHR 1.6 (95% CI: 1.33 – 1.99) • Reduced probability of virological suppression at district and regional hospital compared to PHC: aOR 0.76 (95% CI: 0.59-0.97) and 0.64 (95% CI: 0.56 – 0.75)
Reidy W et al.[10] (2014)	Kenya	• Prospective cohort • Multi-centre • Comparing outcomes at PHFs and SHFs	26690 adults	At least comparable outcomes: • Less LTFU at 6 months post initiation at PHFs (7.4% vs. 4.7%) • No significant difference in mortality between PHFs and SHFs
Paediatrics				
Bock P et al.[12] (2008)	South Africa: Western cape	• Retrospective cohort • Comparing outcomes at PHC facilities, level 1 hospitals and level 2 & 3 hospitals	1741 children <15yrs old	At least comparable outcomes: • Less attrition at PHCs and district hospitals than level 2&3 – not significant • No significant difference in LTFU at 6 &12 months • No significant difference in viral suppression
Fayorsey R et al. [13] (2013)	5 Sub-Saharan African countries	• Retrospective analysis • Multi-centre • Comparing outcomes at PHFs and SHFs	8475 children < 15yrs old	Better outcomes at PHFs: • Less LTFU at 12 months post initiation at PHFs (9.8/100 PYs) than SHFs (20.2/100PYs) • Lower mortality rates at PHFs (5.2/100PYs) than SHFs (6/100PYs)
Outcomes after down-referral:				
Adults				
O'Connor C et al.[14] (2011)	South Africa: Johannesburg	• Retrospective cohort • Single-centre • Reporting on outcomes of down-referred patients	3361 adults	• High rates of retention in care post down-referral (95%) • Of those patients LTFU – 58% lost at the point of down-referral
Brennan A et al.[15] (2011)	South Africa Johannesburg	• Retrospective matched cohort • Single centre • Comparing outcomes of down-referred patients to a matched 'retained in care' cohort	2772 adults: 693 down-referred 2079 retained at initiation site	Better outcomes in down-referred group: • Lower rates of LTFU: 1.4% vs. 4.2% at 12 months of follow up • Lower mortality rates: aHR 0.2 (95% CI: 0.04 – 0.8) • Lower rates of viral rebound: 3.3% vs. 5.6% at 12 months of follow up
Long L et al.[16] (2011)	South Africa Johannesburg	• Retrospective matched cohort • Single centre • Comparing outcomes of down-referred patients to a matched 'retained in care' cohort	2848 adults: 712 down-referred 2136 retained at initiation site	Better outcomes in down-referred group: • Comparably high rates of retention in care (>90% in both groups) • Less attrition in down-referred group: RR 0.27 (95% CI: 0.15 – 0.49) • Cost saving of 11% in down-referred group • High rates of referral back to treatment initiation site in down-referred group (17% in 12 month)

Study	Setting	Design	Study population	Outcomes
Outcomes after down-referral:				
Adults				
Grimsrud A et al. [17] (2014)	South Africa Cape Town	• Prospective cohort • Single centre • Comparing outcomes of patients down-referred to nurse-managed clinic to those retained at doctor-managed clinic.	5746 adults: 2341 down-referred 3405 retained at treatment initiation site	• Higher rates of LTFU in down-referred group: aHR 1.36 (95% CI: 1.09 – 1.69) • Comparable rates of mortality: aHR 1.51 (95% CI: 0.9 – 2.55) Comparable rates of virological failure: aHR 0.94 (95% CI: 0.78 – 1.13)
Auld AF et al. [18] (2015)	Swaziland	• Retrospective cohort study • Multi-centre • Comparing outcomes of patients initiated and maintained on ART at central initiation facilities (hubs), those down-referred to PHCs (spokes), and those initiated and maintained at PHC clinics	2510 adults: 367 down-referred 1149 retained at 'hubs' 483 initiated at hubs with no associated 'spokes' 511 initiated at 'spokes'	Better outcomes at PHC clinics: Of those initiated at 'hubs', better outcomes in down-referred group than maintained group: • Lower rates of LTFU aHR 0.35 (95% CI: 0.29 – 0.5) • Lower rates of attrition aHR 0.50 (95% CI: 0.34 – 0.76) • Comparable rates of mortality Better outcomes in those initiated at 'spokes' vs. those initiated and maintained at 'hubs' • Lower rates of LTFU: aHR 0.59 (95% CI: 0.45 – 0.77) • Lower rates of attrition: aHR 0.60 (95% CI: 0.47 – 0.77) Comparable rates of mortality
Paediatrics				
Hansudewechakul R et al.[21] (2012)	Thailand	• Retrospective cohort • Single paediatric HIV care network (1 tertiary hospital, 16 community hospitals) • Intensive community support post down-referral • Comparing outcomes of down-referred patients to a 'retained in care' cohort	410 Children: 169 down-referred 241 retained in 3° care Median age at initiation: 8.6 years	Comparable outcomes post down-referral: • No LTFU in study period in either group • No difference in rate of improvement in CD4% or WAZ score • 3.5% down-referred patients referred back to 3° care
Morsheimer M et al.[22] (2012)	South Africa Cape town	• Retrospective cohort • Multi-site (7 PHC clinics) • Comparing outcomes of down-referred patients to those who initiated ART at PHC	613 Children: 343 initiated at PHC 270 down-referred Median age at initiation: 2.2 years	Comparable outcomes: • No difference in mortality once PHC initiates were on ART >6 months • Virological suppression attained within 6 months in 77% of patients down-referred with unsuppressed viral loads. • Low rates of referral back to 3° care: 0.37%

Study	Setting	Design	Study population	Outcomes
Outcomes after down-referral:				
Both				
Yu J et al.[20] (2008)	Malawi	• Retrospective cohort • Single-centre • Comparing outcomes of down-referred patients to a 'retained in care' cohort	4175 patients: 805 down-referred 3370 retained in care Included 477 children (11% of cohort)	At least comparable outcomes: • No significant difference in rates of LTFU or retention in care. • Lower rates of mortality in down-referred group (5% vs. 12.5% p<0.001) • Median interval between down-referral and transfer-in to new site 1.3 months – therefore likely no treatment interruption during transfer process
Chan A et al.[19] (2010)	Malawi	• Retrospective cohort • Single-centre (1 tertiary hospital, 16 rural health centres) • Comparing outcomes of down-referred patients to a 'retained in care' cohort	8093 patients 3440 decentralized Included 778 children (10% of cohort)	Better outcomes in down-referred group: • Lower rates of LTFU: aOR 0.48 (95% CI: 0.40 – 0.58) • Lower rates of mortality: aOR 0.19 (95% CI: 0.15 – 0.25)
Systematic review				
Kredo T et al.[7] (2013)	LIMC	• Systematic review • 16 studies included (15 from Africa) • 14 cohort studies, 2 cluster randomised trials	39090 patients (for analysis of 'partial decentralization')	Best outcomes associated with 'partial decentralisation' – treatment initiation at hospital level with subsequent down-referral: • Lowest rates of attrition: RR 0.46% (95% CI: 0.29 – 0.71) – moderate quality evidence • Lower rates of LTFU: RR 0.55 (95% CI: 0.45 – 0.69)

PHC: Primary healthcare. ***PHF***: Primary health facility ***SHF***: Secondary/tertiary health facility ***aHR***: adjusted hazards ratio ***aOR***: adjusted odds ratio ***LIMC***: Lower- and middle-income countries

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Chapter 2: Publication Ready Manuscript

Title Page

Short term outcomes of down-referral in provision of paediatric antiretroviral therapy at Red Cross War Memorial Children's Hospital, Cape Town: A retrospective cohort study.

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Abstract

Background: The large scale-up of paediatric HIV care necessitated down-referral of many children receiving antiretroviral therapy (ART) from Red Cross War Memorial Children's Hospital (RCWMCH). No published data exists on the outcomes of these children.

Objectives: To assess clinical, immunological and virological outcomes of children receiving ART in the first 12 months after down-referral to primary health care (PHC) clinics, and identify determinants of successful down-referral.

Methods: We conducted a retrospective cohort study of children <15 years of age who commenced ART at RCWMCH and were subsequently down-referred to one of two PHC clinics between January 2006 and December 2012. Baseline characteristics of patients and caregivers as well as CD4 counts, viral loads and weights were collected at 6 and 12 months post-down-referral. Outcomes included retention in care and viral suppression.

Results: One hundred and sixteen children down-referred to Heideveld and Gugulethu were included. After down-referral 13.8% of the cohort never arrived at the designated clinic, and 10% took longer than 8 weeks, therefore probably experiencing treatment interruption. At 12 months post down-referral only 68.2% remained in care at the designated clinics. No factors were associated with retention in care. For those children who remained in care at the PHC clinics, the clinical and immunological gains achieved prior to down-referral were sustained through 12 months of follow up, and 54.7% of the retained cohort had documented viral suppression at 12 months.

Conclusion: Down-referral of children on ART is a vulnerable process with risk of loss to follow-up and treatment interruption.

The HIV/AIDS epidemic has had a dramatic impact on the health of South Africa's children, contributing substantial morbidity and mortality. Without antiretroviral therapy (ART) it is estimated that more than 50% of perinatally infected children will die before their second birthday.[1] The South African national ART programme was launched in April 2004, and is now the biggest programme in the world with over 3 million people receiving ART, including an estimated 160 000 children. Since its inception, the national ART programme has grown rapidly, and resulted in substantial positive change. Through improvements in the prevention of mother-to-child transmission (PMTCT) programme, vertical transmission was reduced from 15% in 2009 to 4% in 2014, averting an estimated 370 000 new childhood HIV infections.[2] The 2013 national guidelines further expanded paediatric access to ART by broadening initiation criteria to include all HIV-infected children younger than 5 years of age. By 2014 almost half of all HIV-infected children in the country were accessing ART, an increase from just 11% in 2009.[2]

In the push for rapid scale-up of ART provision and improvement in ART coverage, the South African government adopted a public health approach to HIV care. Central to this approach are two closely linked concepts of task shifting and decentralization. Task shifting entails 'lower' cadres of health care providers, and sometimes non-professionals, taking over responsibilities previously held by doctors or 'higher' cadres of health workers.[3] Decentralizing care includes moving care from tertiary referral centres to health care centres, clinics, and even beyond clinics into communities - closer to patient's places of residence.[4] For many patients this has required a process of down-referral to sites with less specialized health care facilities.

The Western Cape paediatric ART programme has made considerable efforts to decentralize care of HIV-infected children. Between March 2004 and December 2015 the number of clinics in the province treating children with ART increased from 11 to 180, and the percentage of children receiving ART from the three Cape Town tertiary hospitals declined from 78% to 14.7%.[5,6] By 2007/2008 the ART coverage rate in the province had improved to over 95%, well exceeding the national average of 37%.[7] This was a consequence of both significant gains in preventing mother-to-

child-transmission of HIV as well as the expansion of the paediatric HIV programme into primary health care (PHC) settings. This decentralized model of care necessitated down-referral of large numbers of children from tertiary academic hospitals to community-based clinics. There is very little data on the outcomes of down-referred children, and optimal down-referral criteria have not been defined. The down-referred cohort from Red Cross War Memorial Children's Hospital (RCWMCH) specifically, has never been studied. This study therefore assessed ART outcomes of a cohort of children down-referred from RCWMCH to two primary health care clinics and explored determinants of successful down-referral.

Methods

Setting

The study was conducted at RCWMCH as well as two PHC clinics in Cape Town, one in Gugulethu and the other in Heideveld.

RCWMCH is a tertiary facility that serves as a referral centre for the paediatric population of the Western Cape and surrounding provinces. HIV-infected children have been accessing ART through this service since 1998. Since 2006, in accordance with the provincial framework for managing HIV-infected children, clinically stable children have been actively down-referred, mainly to level 1 paediatric HIV clinics within the Cape Metropolitan area. Although down-referral criteria have not been formalized or standardized, attending clinicians are encouraged to identify clinically stable patients for down-referral. Down-referral is facilitated by clinicians telephonically arranging the first PHC clinic appointment and providing caregivers with a written clinical summary for clinic staff.

Both Gugulethu and Heideveld clinics fall within the immediate drainage area of RCWMCH and are less than 10 km apart. Gugulethu clinic is a large, well-established clinic that has been providing a paediatric HIV service since 2003. By comparison, Heideveld is a much smaller clinic, which only began its paediatric ART outpatient service in 2010. Both paediatric HIV clinics are medical officer led.

Study design

The hospital ART database was used to identify all children from the Gugulethu and Heideveld drainage areas who commenced ART at RCWMCH between 1 January 2006 and 31 December 2012. Baseline characteristic of patients and their caregivers were retrospectively extracted from case record forms held by the infectious diseases clinic in order to compare those patients who were subsequently down-referred to the PHC clinics by 31 December 2012 with those who remained in care at RCWMCH.

For the group of patients who had been down-referred to the PHC clinics, hospital folders were reviewed to extract further information relating to hospital admission diagnoses, length of follow up at RCWMH and clinical and virological parameters prior to the point of down-referral. CD4 percentage (CD4%) and viral loads (VLs) prior to down-referral were accepted within a window period of 6 months.

At the PHC clinics data were again retrospectively collected from patient folders, including the time between down-referral and presentation at PHC, as well as outcomes at 6 and 12 months post down-referral. Measures included patient's weight, and CD4% and viral load results. For 6- and 12-month CD4% and viral load results, the closest measure within a window period of 4-8 and 9-15 months respectively were used.

Anthropometric measurements such as weight and height were converted to gender specific weight-for-age z-scores (WAZ), height-for-age z-scores (HAZ) and weight-for-height z-scores (WHZ) scores, according to the 2000 CDC growth charts.[8] Moderate underweight for age, stunting and wasting were defined as WAZ, HAZ and WHZ between -2 and -3 Z-Scores, below -3 were defined as severe underweight, stunting and wasting. Specific outcomes measured at 6 and 12 months post down-referral included mean WAZ, WAZ category, median CD4%, the proportion of children with severe immunodeficiency as defined by the World Health Organization,[9] the proportion who were virologically suppressed (defined as a viral load <400 copies/mL), and at 12 months the proportions who remained in care or had been lost to follow up were documented. Viral load was measured by the Abbott Realtime HIV-1 assay in copies/mL and converted to $\log_{10}$ values, and CD4 absolute counts and percentages were quantified by the PanLeucogated method.[10,11]

Data analysis

Data were collected on a standardized data capture sheet and inputted into Microsoft Excel. Data were analysed using Stata software (Stata/IC 13.0 for Windows, StataCorp LP, USA). Mean ± standard deviation (SD) or median and interquartile range (IQR) were used to describe normally- and non-normally distributed data respectively. Student's t-test was used to compare normally distributed data and Wilcoxon sum rank test for skewed data. Categorical data were compared using chi-squared or Fisher's exact test, as appropriate

Univariate analyses using unadjusted risk ratio (RR) and 95% confidence intervals (95% CI) were performed to identify potential factors associated with retention in care at the PHC clinic at 12 months post down-referral. There were no significant factors on univariate analysis therefore multivariable analyses were not completed.

Ethics considerations

The study was approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town (HREC REF: 246/2013) and the Western Cape Department of Health. Patient consent was not obtained because the data was collected and collated retrospectively. The study was completed in accordance with the Declaration of Helsinki.

Results

A total of 231 children from Heideveld and Gugulethu drainage areas were identified who had initiated ART at RCWMCH within the study time period. Of these, 119 were subsequently down-referred to the PHC clinics for ongoing care. Three down-referred patients were excluded from the analysis; 1 had initiated ART prior to presentation at RCWMCH, and 2 were not actively down-referred but rather lost to follow-up (LTFU). Data from the remaining 116 children (study cohort) were analysed.

Baseline characteristics

The median age of the study cohort at ART initiation was 11 months; 52.6% (61/116) were <12 months of age. Moderate to severe wasting and stunting were present in

29.2% and 39.3% of the cohort respectively. Advanced clinical disease (WHO clinical stage 3 or 4) was present in 90.2% of the cohort. At the time of initiating ART 18.1% (21/116) of the study cohort was on treatment for tuberculosis (TB), 23.8% (5/21) of whom were treated for extra-pulmonary TB. The median CD4% was 17.6%, and 68.7% met the WHO definition of severe immunodeficiency.[9] Baseline characteristics of the study cohort were similar to the characteristics of HIV-infected children from Gugulethu and Heideveld who were initiated on ART at RCWMCH during the study period but were retained in care at the hospital (summarized in Table 1).

The primary caregiver for the majority (87.1%) of children in the study cohort was the mother, whilst 6% were maternal orphans. Less than 40% of mothers received any PMTCT intervention and only 12.9% were receiving ART at the time of their child's initiation. Almost half of the cohort lived in informal housing and 52.6% were accessing government grants. Table 2 summarizes the primary caregiver and social characteristics of the study cohort and non-down-referred children. The only statistically significant difference between these groups was the proportion of literate primary caregivers (66.4% vs. 72.3%, p=0.01). As there was a large amount of missing data for this variable it is unlikely to be clinically significant.

HIV diagnosis and hospitalisation

The majority of the cohort (79/116, 68.1%) had undiagnosed HIV infection prior to referral to RCWMCH, only 19.8% (23/116) were previously diagnosed at a PHC clinic, the remainder having been diagnosed at other hospitals or private doctors. Not all children required hospital admission, 13.9% (16/115) were managed exclusively on an outpatient basis at the outpatient HIV clinic (OHC). For the 99 children who were admitted to hospital, the mean ± SD length of stay was 19 ± 13.7 days and the most common admission diagnoses were acute lower respiratory tract infection (52.5%) and diarrhoeal disease (36.4%). The majority of children were managed in the general medical wards (71/98, 72.4%), however 18.4% required an intensive care unit (ICU) admission during their stay. Of the admitted children, 69.7% (69/99) were initiated on ART during hospitalisation, 15.9% (11/69) of whom whilst still in ICU. The other 30.3% (30/99) initiated ART during follow-up at the OHC.

ART management prior to down-referral

All children in the study cohort were initiated on ART at RCWMCH. The time between HIV diagnosis and ART initiation of these children declined progressively from a median of 414 days for those diagnosed before 2005, to 15 days for those diagnosed in 2011/2012, a decrease of 96.4%.

Of the children who required hospitalisation, 21.2% (21/99) were initiated on ART and down-referred to PHC clinics to continue their treatment at the time of discharge. The remaining 95 children were followed up at the OHC at RCWMCH for a median duration of 320 days (IQR: 189 – 685), with a mean ± SD number of 11.9 ± 8.4 clinic visits prior to down-referral, and 26.6% (25/94) of the cohort having at least 1 hospital admission during follow-up. The median age at down-referral was 25.8 months (IQR: 12.2 - 52.1). At down-referral 72.6% (69/95) of the cohort had a documented viral load within the preceding 6 months. Of these, 79.7% (55/69) were virally suppressed. Five children who had defaulted ART while attending OHC at RCWMCH were down-referred to re-start therapy at the referral clinic.

Outcomes after down-referral

At the PHC clinics folders for 6 patients were not found – so they were excluded from subsequent analysis. Once down-referred, 16 children did not arrive at the designated PHC, accounting for 64% (16/25) of all children LTFU within 12 months of down-referral. Furthermore, although the median time between down-referral and presentation at the PHC was 26 days (IQR: 19.3 – 30.8), 11.7% (11/94) of those who did arrive took longer than 8 weeks (median 73 days, IQR: 64.5 – 106) to present to the PHC clinic. At down-referral 24.5% (27/110) of patients were either LTFU or had a probable treatment interruption.

Twelve months after down-referral 68.2% (75/110) of patients remained in care at the designated PHC clinic, a further 6.4% (7/110) had been transferred out to other clinics and 1.8% (2/110) were back in care at RCWMCH. One patient (0.9%) had died, and 25 others (22.7%) had been LTFU. Of those LTFU, 52% (13/25) were under 12 months of age at the time of ART initiation.

Response to ART at down-referral clinics

The 75 children who remained in care at the designated down-referral clinics showed sustained clinical and immunological response to ART over the 12 months of follow-up (table 3).

The number of children with moderate to severe underweight for age declined steadily from 50.7% (38/75) at initiation to 8% (6/75) 12 months after down-referral, $p<0.001$, and the percentage of children with severe immunodeficiency declined from 69.3% to 1.3%, $p<0.001$. The median CD4% at down-referral had increased from 17% at initiation to 31.2%, $p<0.001$, and this was sustained over 12 months of follow-up in the PHC clinics. Similar rates of viral suppression were documented at down-referral (38/75, 50.7%) and 12 months post down-referral (41/75, 54.7%), $p=0.62$. However, if only those children with documented viral loads are considered, rates of viral suppression were much higher both at down-referral (38/44, 86.4%) and 12 months later (41/54, 75.9%).

Despite these markers of improvement, 14.7% (11/75) of the cohort required at least 1 hospital admission during the first year of follow up after down-referral.

Predictors of Retention in Care

On univariate analysis no significant risk factors of retention in care at the two designated PHC clinics 12 months after ART initiation were identified (Table 4).

Discussion

The present study showed that for children who remained in care at the designated PHC clinics, clinical and immunological gains achieved on ART were sustained for at least 12 months after down-referral, and were consistent with results from larger studies in similar cohorts.[12,13] It has also shown, however, significant negative outcomes associated with the down-referral process – with 22.7% of the study cohort LTFU, 64% of whom never presented to the designated referral clinics and a further 11.7% delaying their initial clinic appointment by a median of 73 days. In a study conducted in Thailand, of 168 children down-referred from a tertiary hospital to several community hospitals, none were LTFU during a median follow-up time of 18

months.[14] This perfect retention in care can be attributed to the intensive support and adherence counseling provided after down-referral, ongoing involvement of the referral team who provided active mentorship and clinical support to the treating teams in the community hospitals as well as 6-monthly clinical reviews of the down-referred children at the tertiary referral hospital.[14] By contrast, the support available in our study was much less intensive, consisting of telephonic support for clinicians caring for HIV-infected children at the PHC clinics, and monthly clinical mentoring visits by an infectious diseases sub-specialist from RCWMCH.

Another difference between our study and the Thai study is the age of the children. In the Thai study, the median age at initiation was 8.6 years compared to 11.0 months for our cohort. In a study of more than 5000 infants (<12 months of age) initiated on ART in Southern Africa, the 3-year mortality and LTFU estimates were 16% and 29% respectively.[13] These results suggest that HIV-infected infants remain extremely vulnerable during the initial period on ART. Given that more than 50% of the down-referred children were infants at ART initiation this may partly explain the LTFU prevalence in our study.

Movement of patients between Cape Town and other parts of South Africa without the knowledge of the attending clinician is a common occurrence. This is another possible factor contributing to LTFU in our study. It is possible that some of the LTFU children continued care at other HIV clinics in Cape Town or in the rest of South Africa. Our results suggest that the process of transitioning care from one site to another is inherently vulnerable, therefore greater attention should be given to monitoring down-referred children and strengthening the support provided to them and their caregivers. This could be done through more formalized communications with referral sites or even telephonic contact tracing of patients after down-referral.

In order to minimize risks associated with down-referral it is imperative that we try to understand the factors that contribute to a successful transfer and those that hinder this process. Unfortunately our study did not identify any specific factors associated with successful down-referral. An early study examining adult patient attitudes to decentralized HIV care raised concerns over confidentiality and stigma associated with treatment within the community.[15] Whilst no similar data exists for the

paediatric population, the issues of stigma and confidentiality are likely equally as important for the caregivers on whom they rely to take them to clinic for treatment. Further studies are needed to clarify whether this does indeed affect the success of down-referral in provision of paediatric ART. Other factors that could be explored include distance to PHC clinic and formal down-referral criteria.

Study strengths and limitations

To our knowledge this is the first South African study that has followed a cohort of children receiving ART through the process of down-referral from a tertiary referral hospital to PHC clinics. It therefore provides a unique perspective on the impact of the down-referral process on paediatric ART provision under routine operational conditions.

There are a number of limitations to this study. The small cohort size may have limited the ability to detect significant factors affecting retention in care. Secondly this study only looked at two of the PHC clinics that fall under RCWMCH drainage area, consequently the results are not necessarily generalisable. Furthermore, the study design did not allow for tracing of patients who were LTFU. It is possible that after down-referral some patients may have continued care at a PHC clinic other than the one they were referred to. If this were the case the study would have over emphasized negative outcomes of down-referral.

Conclusion

This study has shown that the greatest risk of LTFU and treatment interruption associated with down-referral in provision of paediatric ART occurs at the point of down-referral. Children who successfully navigate this transition in care show sustained clinical and virological improvements.

Conflicts/disclosures. The authors declare no conflict of interest

Authors' contributions. JC drafted the study protocol, collected and analysed the data, and drafted the manuscript. PA assisted with extraction of data from the RCWMCH database and patient folders. BE conceived the study, participated in the data analysis and drafting of the manuscript. All authors read and approved the final manuscript.

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Tables and Legends

Table 1: Patient characteristics prior to antiretroviral therapy initiation

	Study group	Non down-referred group	*p*-value
Number	116	112	
Gender, n (%) Female Male	N=116 71 (61.2) 45 (38.8)	N=112 61 (54.5) 51 (45.5)	0.3
Age at initiation (in months), median (IQR)	N = 116 11.0 (3.8 – 38.3)	N=112 8.2 (3.7-50.6)	0.98
WAZ, mean ± SD	N=116 -2.06 ± 1.6	N=111 -2.4 ± 1.7	0.18
WAZ categories, n (%) Mild – normal Moderate underweight Severe underweight	N= 116 55 (47.4) 31 (26.7) 30 (25.9)	N=111 51 (45.9) 26 (23.4) 34 (30.6)	0.82
HAZ, mean ± SD	N=107 -1.8 ± 1.6	N=77 -1.8 ± 1.6	0.9
HAZ categories, n (%) Mild-normal Moderate stunting Severe stunting	N=107 65 (60.7) 23 (21.5) 19 (17.8)	N=77 48 (62.3) 14 (18.2) 15 (19.5)	0.83
WHZ, mean ± SD	N=106 -1.2 ± 1.8	N=66 -1.7 ± 2.5	0.14
WHZ categories, n (%) Mild-normal Moderate wasting Severe wasting	N=106 75 (70.8) 17 (16) 14 (13.2)	N=66 41 (62.1) 9 (13.6) 16 (24.2)	0.24
WHO stage, n (%) 1 2 3 4	N = 112 4 (3.6) 7 (6.3) 50 (44.6) 51 (45.5)	N=112 5 (4.5) 12 (10.7) 46 (41.1) 49 (43.8)	0.65
CD4 absolute count, median (IQR)	N=115 585 (249 – 1067)	N=112 460.5 (240 – 1119.5)	0.77
CD4%, median (IQR)	N=115 17.6% (11,4 – 23)	N=112 17.5% (10.6 – 24.3)	0.81
% Severe immunodeficiency, n (%)	N=115 79 (68.7)	N=112 79 (70.5)	0.76
Log_{10} viral load, median (IQR)	N=101 5.6 (5 – 6.4)	N=105 5.9 (5 – 6.6)	0.38
Immunisations up to date, n (%)	N= 100 86 (86)	N=91 71 (78)	0.15

Table 2: Mother, primary caregiver and social characteristics at antiretroviral therapy initiation

	Study group	Non down-referred group	*p*-value
Mother Alive, n (%)	N= 116	N= 112	
Yes	109 (94)	99 (88.4)	0.12
No	7 (6)	12 (10.7)	
Unknown	0	1 (0.9)	
Maternal PMTCT prophylaxis, n (%)	N=116	N=112	
HAART	3 (2.6)	4 (3.6)	0.19
Non-HAART	38 (32.8)	30 (26.8)	
None	65 (56)	53 (47.3)	
Unknown	10 (8.6)	25 (22.3)	
Mother on ART, n (%)	N= 116	N= 112	
Yes	15 (12.9)	15 (13.4)	0.05
No	89 (76.7)	73 (65.2)	
Unknown	12 (10.3)	24 (21.4)	
Primary caregiver relationship to child, n (%)	N=116	N=112	
Mother	101 (87.1)	91 (81.3)	0.23
Grandmother	10 (8.6)	6 (5.4)	
Other	5 (4.3)	11 (9.8)	
Unknown	0	4 (3.6)	
Primary caregiver literate, n (%)	N= 116	N=112	
Yes	77 (66.4)	81 (72.3)	0.01
No	4 (3.4)	5 (4.5)	
Unknown	35 (30.2)	26 (23.2)	
Housing type, n (%)	N=116	N=112	
Formal	62 (53.4)	67 (59.8)	0.33
Informal	53 (45.7)	38 (33.9)	
Unknown	1 (0.9)	7 (6.3)	
Household treatment supporter, n (%)	N=116	N=112	
Yes	67 (57.8)	70 (62.5)	0.46
No	31 (26.7)	22 (19.6)	
Unknown	18 (15.5)	20 (17.9)	
Accessing grant, n (%)	N=116	N=112	
Yes	61 (52.6)	58 (51.8)	0.9
No	49 (42.2)	48 (42.9)	
Unknown	6 (5.2)	6 (5.4)	

Table 3: Longitudinal changes of the 75 children who remained in care at the designated down-referral clinics 12 months after down-referral

	Initiation	At down-referral	6 Months after down-referral	12 Months after down-referral
CD4%, median (IQR)	N= 75 17 (10.9–23)	N= 45 31.2 (22.8-37.1)	N=54 32.5 (25.5-38.7)	N=45 32 (27.3-35.3)
Suppressed Viral Load, n (%) Yes No Unknown/ not done	N= 75 0 (0) 67 (89.3) 8 (10.7)	N= 75 38 (50.7) 6 (8) 31 (41.3)	N=75 47 (62.7) 13 (17.3) 15 (20)	N=75 41 (54.7) 13 (17.3) 21 (28)
Severe immunodeficiency, n (%) Yes No Unknown	N=75 52 (69.3) 23 (30.7) 0 (0)	N=75 4 (5.3) 41 (54.7) 30 (40)	N=75 6 (8) 48 (64) 21 (28)	N=75 1 (1.3) 49 (65.3) 25 (33.3)
WAZ mean ± SD	N= 75 -2.03 ±1.6	N= 62 -0.8 ±1.4	N=71 -0.3 ±1,2	N=71 -0.3 ±1,2
WAZ categories, n (%) Mild – normal >-1 Moderate -2 - -3 Severe <-3 Unknown	 37 (49.3) 19 (25.3) 19 (25.3) 0 (0)	 54 (72) 5 (6.7) 3 (4) 13 (17.3)	 66 (88) 4 (5.3) 1 (1.3) 4 (5.3)	 65 (86.7) 5 (6.7) 1 (1.3) 4 (5.3)

Table 4: Predictors of retention in care at the designated PHC clinic, 12 months after down-referral

Risk Factor	RIC	Not RIC	Unadjusted RR [95% CI]
Age <12 months at ART initiation	41/75	19/35	1.01 [0.70 – 1,45]
Advanced clinical disease (WHO stages 3 & 4) at ART initiation	66/73	30/33	0.99 [0.87 – 1.13]
Moderate or severe underweight at ART initiation	38/75	20/35	0.89 [0.62 – 1.28]
TB co-infection at ART initiation	12/75	4/35	1.40 [0.49 – 4.03]
Up-to-date immunization status at ART initiation	58/66	24/30	1.10 [0.90 – 1.34]
ART initiation as hospital inpatient	47/75	21/35	1.04 [0.76 – 1.44]
Mother as primary caregiver at ART initiation	63/75	31/35	0.95 [0.81 – 1.11]
Formal (vs informal) housing at ART initiation	43/75	19/35	1.06 [0.74 – 1.52]
Caregiver receiving grant at ART initiation	40/72	15/32	1.19 [0.78 – 1.81]
Household treatment supporter at ART initiation	46/66	18/28	1.08 [0.79 – 1.49]
Follow-up at RCWMCH for >6 months prior to down-referral	50/75	21/35	1.11 [0.81 – 1.52]
Suppressed viral load prior to down-referral	38/44	15/22	1.27 [0.93 – 1.73]
Mother alive at 12 months post-down-referral	54/67	12/13	0.87 [0.72 – 1.06]

RIC = retained in care

Chapter 3: Appendices

Appendix 1: The protocol

Introduction

In September 2000, the South African government along with 188 other member states signed the United Nations Millennium Declaration. As part of the Millennium Development Goals the government thereby committed to reduce by two thirds the under-five-mortality-rate (U5MR) between 1990 and 2015[1]. According to figures from both the UN and the Actuarial Association of South Africa (ASSA) the U5MR increased from 1990, peaked around the year 2000, and thereafter followed a slowly declining trend. Although there is ongoing controversy over the accuracy of these figures[2] there is agreement that the current U5MR (estimated at 56/1000 live births[3]) remains unacceptably high, and far off the goal of 20/1000 by 2015. Furthermore, there is no longer any disagreement over the profound contribution the HIV/AIDS epidemic makes in hindering progress towards reducing childhood mortality. In a speech to the National Assembly in May 2011, the Minister of Health, Dr Aaron Motsoaledi, attributed 35% of childhood mortality to HIV and AIDS[4]. In this same speech he briefly outlined government efforts and plans to address this "unacceptably high maternal and child mortality."

Government response to the HIV/AIDS epidemic is now firmly based on a public-health approach to scaling up provision of Antiretroviral therapy (ART) as advocated by the World Health Organization (WHO). One of the central features of this approach is the decentralisation of care[5]. Between February 2010 and May 2011 the number of health centres providing ART in South Africa increased from 490 to over 2200 and the number of nurses certified to provide ART increased from 250 to 2000[4]. This expansion and decentralisation of ART provision facilitated the increase in the number of people receiving ART from 923 000 to over 1,4 million in the same time period. The paediatric population has historically been under-represented in those receiving ART. Recent data, however, suggests that paediatric coverage (defined as the number of children under 15 years commencing treatment in a given year divided by the estimated number of new paediatric infections in that same year) has improved

substantially from 2% in 2002/2003 to 36% in 2007/2008[6]. This reflects both the successes of the Preventing Mother to Child Transmission (PMTCT) programme as well as greater access to ART for the paediatric population. By the end of 2010 there was an estimated 108 682 children under the age of 15 receiving treatment, making the South African paediatric ART programme the largest in the world[7]. According to the WHO global report , this represented only an estimated 36% coverage. The ability to reach the government stated goal of initiating 80% of those in need and retaining 70% of them in treatment at 5 years after initiation[8], will depend heavily on the policy of 'down-referral' and decentralisation.

As the rollout of ART in South Africa reaches ever-increasing numbers of people, so the focus on 'task-shifting' or decentralising care increases[9]. Furthermore, as the sustained survival benefits of treatment are realised, so the call to manage HIV as a chronic illness in primary healthcare (PHC) facilities grows[10]. Over the last few years the Western Cape Paediatric ART programme, in line with government policy, has been actively down-referring stable patients to PHC facilities. Between March 2004 and September 2006 the percentage of children receiving their ART from the three Cape Town academic hospitals declined from 78% to 38%, and the number of clinics treating children with ART increased from 11 to 41[11]. By July 2012, less than 14% of children were still receiving treatment from tertiary hospitals and the number of clinics treating children with ART had increased to 134[12]. In a retrospective review of over 1700 children commenced on ART in the Western Cape, Bock et al. demonstrated comparable rates of loss to follow up and virological suppression between children managed in PHC facilities and those in tertiary care[13]. There are however, very few studies that have specifically assessed the effects and outcomes of the down-referral process.

Data from the adult literature have revealed a reluctance of patients to be down-referred. In a study assessing patient attitudes to decentralisation, despite acknowledging the advantages of down-referral, namely savings of time and transport costs, patients still preferred attending a centralised treatment centre. They cited lack of confidentiality and poor nurse attitudes at local clinics as well as availability of ancillary services at the central hospital[14]. Despite this finding, comparable short-term outcomes of adult's down-referred from a tertiary hospital to PHC's have been

demonstrated in a similar population in Soweto[15]. In this matched cohort analysis patients became eligible for down-referral after 11 months of treatment if they were clinically well, with undetectable viral loads, CD4 cell counts ≥ 200cells/μl and no opportunistic infections. Over 65% of eligible patients were not down referred – and it is unclear as to whether this is because they refused or were not offered down-referral. Although the outcomes of this study seem encouraging, data presented at the 16th International Workshop on HIV Observational Databases, showed a concerning increase in mortality in patients 'transferred out' from one level of care to another. In this cohort of 20116 patients (again an adult population) the mortality amongst those transferred out was 43% compared to 29% in the lost to follow up group[16]. Thus there are many remaining unanswered questions with regards to the outcomes of down-referral in the adult population – let alone the paediatric one.

In the last 6 years (2006-2011) 1214 children have been initiated on ART at Red Cross Children's War Memorial Hospital (RCWMCH), and 1260 were down referred to level 1 clinics for ongoing care. To date there has been no assessment of the outcomes of this group of children and the decision to down-refer is done on a case-by-case basis at the clinician's discretion. This study aims to assess the short-term outcomes of recently down-referred patients with the hope of establishing the safety and efficacy of the current programme of decentralisation of ART provision currently under way at RCWMCH.

Aim

- To describe the short-term outcome of HIV-infected children who were initiated on antiretroviral therapy at Red Cross War Memorial Children's Hospital and recently down-referred to their local primary health care clinics for ongoing care

Objectives:

- To describe the clinical status and antiretroviral control of children prior to down-referral
- To describe the clinical and virological status of children during the first 6 – 12 months after down-referral

- To identify risk factors of successful down-referral

Methods:

Setting:

The study will be done at Red Cross War Memorial Children's Hospital (RCWMCH) as well as two primary health care clinics – Gugulethu and Heideveld.

RCWMCH is a 270 bed tertiary facility that serves as a referral centre for the paediatric population of the Western Cape and surrounding provinces. In 1990 an infectious diseases (ID) clinic was established at the hospital, and since 1998, HIV positive children have been accessing antiretroviral therapy (ART) through this service. More than 1900 children have been initiated on ART. Since 2006, in accordance with the provincial framework for managing HIV-infected children, clinically stable children have been actively down-referred, mainly to level 1 clinics within the Cape Metropolitan area.

The timing of down-referral has been left to the attending clinician, who decides when a child is sufficiently clinically stable to be managed at a level 1 facility. Children deemed to be clinically unstable or who require sub-specialist care are retained by the ID service at RCWMCH.

The immediate drainage areas of RCWMCH are the Klipfontein and Mitchells Plain sub-districts. Since 2010 RCWMCH has been actively supporting paediatric HIV clinics in the Klipfontein sub-district. Both the Gugulethu and Heideveld HIV clinics fall within this sub-district. Both clinics are less than 10 km apart. Gugulethu clinic is a large, well established clinic with support from a local Non Governmental Organisation (NGO). By comparison, Heideveld is a much smaller clinic which only began its paediatric ART programme in 2010. At the end of July 2012, Gugulethu and Heideveld clinics managed 390 and 41 children on ART, respectively.

Study design & population

Descriptive analysis of short term outcomes of all HIV-infected children commenced on ART at RCWMCH between 1 January 2006 and 31 December 2012 and who were subsequently down-referred to either Gugulethu or Heideveld clinics.

Study Plan:

1. Using the hospital HIV database, identify all HIV-infected children, from the Heideveld and Gugulethu drainage areas, who commenced ART during the study period (1/1/2006 – 31/12/2012)
2. Of this initial cohort – identify all patients who had subsequently been down referred for ongoing care by 31/12/2012 – the study group.
3. Assessment of baseline characteristics, comparing the study group to those children from the same areas that remained in care at RCWMCH at the end of the study period.
4. For patients in the study group:
    - Hospital folder review – completing sections A and B of patient data sheet (see appendix A)
    - Clinic folder review (at Heideveld and Gugulethu PHC's) to complete section C of patient data sheet.
5. Analysis of data and description of findings

Data collection and entry:

Data will be collected from the hospital's HIV database and hospital records. This will allow for a comparison of baseline characteristics (including clinical, virological and social characteristics) between those patients who were down-referred in the study time period, and those who were retained in care, as well as a description of care before down-referral

At Gugulethu and Heideveld clinics data will be collected on all the down-referred children from RCWMCH ART programme during the study period. Data collected will focus on compliance (measured by viral load and clinic attendance), retention in care, clinical characteristics (weight, intercurrent illnesses) and social parameters (e.g. relationship to primary caregiver, health of primary caregiver, distance to clinic). Refer part C of the data collection sheet.

Data will be entered anonymously into an excel spreadsheet for analysis.

Data analysis:

The data will be analysed using descriptive measures and conventional parametric and non-parametric comparative statistical methods.

Outputs

The analysed data will be presented at departmental meetings and scientific conferences, and be submitted for peer-review publication.

This project will be used to complete an MMed (Paediatrics) by publication through the University of Cape Town

Ethical considerations

The study will be submitted for approval to the Departmental Research Committee, School of Child and Adolescent Health, University of Cape Town, the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town, and the Western Cape Department of Health. Permission to access patient records at the level 1 clinics will be obtained form the operational manager in the Klipfontien sub-district as well as the clinic managers.

The study will be done in accordance with the Declaration of Helsinki.

Since the data is being collected retrospectively, consent will not be obtained from parents/legal guardians.

The data sheets will include the names/folder numbers of patients to enable the researchers to check information from the hospital folders after data collection has been completed. Each name/folder number will be linked to a study number. Study numbers (but not names/folder numbers) will be entered on an electronic database for anonymous analysis and reporting.

Risks to participants

There are no risks to the participants in this study. Data will be collected retrospectively and all analysis will be done anonymously.

Benefits to participants

There are no direct benefits to the patients included in the study.

Anticipated gain in scientific knowledge

This study should contribute to understanding the down-referral process for HIV-infected children initially treated at RCWMCH and identify factors associated with poor outcomes / lost-to-follow-up. The study may contribute to improving the down-referral process.

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APPENDIX A: PATIENT DATA SHEET

Patient Data Sheet					
Study Number					
Folder Number					
Name					
Date of birth			Gender		
Address					
Initial admission - enrollment into service					
HIV Diagnosis	Rapid	PCR	Unknown		
	First Diagnosis		Previous Diagnosis		
	Date		Date		
	Place		Place		
			Previous ART		
PMTCT	None		NVP		
	AZT/NVP		HAART		
	Unknown				
Clinical Information	Age				
	Immunisations UTD		Yes	No	Unknown
Anthropometry	Weight	_____kg	____Z score	_____%EWFA	
	Height	_____cm	____Z score	_____%EHFA	
	Wasting		____Z score	_____%EWFH	
	Normal	Mild	Moderate	Severe	
Staging	Clinical	1	2	3	4
	CD4		_____%	Date	
	Viral Load		____log	Date	
Hospital Stay	Admision Date:		Discharge Date		
	Duration:				
	Admission diagnosis:				
	Additional diagnoses:				
	Place of care:		S11	Ward	ICU
Tuberculosis:	Mantoux:	Positive		Negative	Unknown
	Induced Sputa		1	2	
	Gastric Washings		1	2	
	CXR				
	Confirmed	Presumed	Excluded	Not investigated	
	Pulmonary	CNS	Disseminated		

	Start date of TX:				
	Regime:				
ART Initiation:	Date of initiation:				
	Place of initiation:		Ward	ICU	ID clinic
	No. counselling sessions completed:				
	Concerns raised during counselling:			Y	N
	Time from Dx to initiation:				
	Time from initiation to discharge:				
	ART Regime:				
Social Information:	Mother:	Name_____			
	Alive:	Y	N	DOD:	Unknown
	ART:	Start date		None	
		Collection clinic:			
	Primary care giver				
	Name:				
	Age:				
	Relationship				
	Literate:				
	Household				
	Dwelling:	Formal	Informal		
	No of adults in house				
	Other ART treatment support in house:			Yes	No
	Household income				
	Grants	CSG	CDG	None	

Section B: Out Patient RXH Follow up					
Clinic Appointments	First Appt date:				
	No. of missed clinic appointments:				
	No. of appointments prior to down referral:				
Concerns during follow up:	Adherence				
	Care giver concerns				
	Social				
	Clinical				
Hospital admissions during follow up:	Dates:	1.			
		2.			
		3.			
	Place:	1.			
		2.			
		3.			
	Diagnosis:	1.			
		2.			
		3.			
New diagnoses during follow up:					
Other medical illnesses:	Active medical diagnoses:				
	1		2		
	3		4		
	5		6		
	7		8		
	Follow up at other RXH clinics:				
	1		2		
	3		4		
	Medications other than ART:				
	1		2		
	3		4		
Virological status during follow up					
	Date	ART month	CD4	%	viral load
Clinical status at down referral	Active medical diagnoses				
	1		2		3
	4		5		6
	Current ART regime				
	Weight	_____kg	____Z score	_____%EWFA	
	Height	_____cm	____Z score	_____%EHFA	
	Wasting		____Z score	_____%EWFH	
	Normal	Mild	Moderate	Severe	

Down referral:	Date of last RXH appt			
	Date of 1st clinic appt given			
	Clinic referred to:		1. Heideveld	2. Gugulethu
Current Social information				
	Primary care giver			
	Name:			
	Age:			
	Relationship			
	Literate:			
	Mother			
	Alive	Yes	No	Date of death
	On ART	Yes	No	Clinic:
	Grants	CSG	CDG	None

Section C: Referral clinic Data						
Clinic referred to:		1. Heideveld		2. Gugulethu		
Care giver recieiving treatment from a clinic		1. Same clinic		2. Other clinic		
		3. Unkonwn		4. None		
Dates of clinic visits		1		2		
		3		4		
		5		6		
		7		8		
		9		10		
n		11		12		
Medications dispensed		Current ART Regime				
		Other chronic meds				
Clinical Status						
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
	Date		Wt (kg)		Ht (cm)	
Hospital admissions during follow up:			Dates:	1.		
				2.		
				3.		
			Place:	1.		
				2.		
				3.		
			Diagnosis:	1.		
				2.		
				3.		
New diagnoses during follow up:						
Virological status during follow up						
		Date	ART month	CD4	%	viral load

Latest Social information				
	Primary care giver			
	Name:			
	Age:			
	Relationship			
	Literate:			
	Mother			
	Alive	Yes	No	Date of death
	On ART	Yes	No	Clinic:
	Grants	CSG	CDG	None

Meds dispensed:	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	
Date	

Appendix 2: Ethics approval, renewal & Permissions

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

02 May 2013

HREC REF: 246/2013

Dr J Copelyn
c/o Prof B Eley
Paediatric Medicine
Red Cross War Memorial Children's Hospital

Dear Dr Copelyn

PROJECT TITLE: SHORT TERM OUTCOMES OF DOWN REFERRAL IN PROVISION OF PAEDIATRIC ANTIRETROVIRAL THERAPY

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year till the 15th May 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

s.thomas

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/05/2017
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	11/5/16

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	9 May 2016		
HREC REF Number	246/2013	Current Ethics Approval was granted until	15 May 2016
Protocol title	Short Term Outcomes of Down-referral in Provision of Paediatric Antiretroviral Therapy		
Principal Investigator	Dr Julie Copelyn		
Department / Office Internal Mail Address	Julie_copelyn@yahoo.com		
1.1 Does this protocol receive US Federal funding?		11 MAY 2016	☑ No

2. Protocol status (tick ✓)

	Research-related activities are ongoing
☑	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		120
Total number of records or specimens collected, reviewed or stored since last progress report		0
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.		☑ No

4. Signature

Signature of PI		Date	9 May 2016

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT

REFERENCE: RP 170/2013
ENQUIRIES: Ms Charlene Roderick

Red Cross Childrens Hospital
Klipfontein road
Rondebosch
Cape town

For attention: **Dr Julie Copelyn and Prof. Brian Eley**

Re: Short Term Outcomes of Down Referral in Provision of Paediatric Antiretroviral Therapy

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact **Ms K Rix on 021 370 5007** to assist you with any further enquiries in accessing the following sites:

Gugulethu CHC

Heideveld CHC

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. The reference number above should be quoted in all future correspondence.

We look forward to hearing from you.

Yours sincerely

DR NT Noleti
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 8/11/2013
CC **P OLCKERS** **DIRECTOR: MITCHELLS PLAIN / KLIPFONTEIN**

Page 1 of 1

Appendix 3: Instructions to Authors (SAMJ)

http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines

Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields.

References should be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*

Scientific letters will be considered for publication as shorter ***Research articles***.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the *SAMJ* peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minumum.

Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ*; the costs of which must be covered by sponsorship or advertising. The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.*

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached individually as '**supplementary files**' upon submission (not solely embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES

References must be kept to a maximum of 15. Authors must verify references from original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by **CrossRef**.

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

PROOFS

A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

CHANGES OF ADDRESS

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

CPD POINTS

Authors can earn up to 15 CPD CEUs for published articles. Certificates may be requested after publication of the article.

CHARGES

There is no charge for the publication of manuscripts.

Please refer to the section on '*Guidelines*' regarding the publication of supplements, where a charge may be applicable.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).