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Characteristics of adult patients who are lost to follow-up in antiretroviral roll out clinics – Gauteng, South Africa

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PART 1

1.1 Introduction

The global commitment by governments throughout the world to scaling up access to Antiretroviral Therapy (ART) in response to the crisis imposed by the HIV epidemic has resulted in a large number of people living with Human Immune-deficiency Virus (HIV) worldwide. According to statistics provided by the World Health Organization (WHO), there were approximately 35 million people living with HIV (PLWHIV) in 2012.[1]This large number of PLWHIV observed in recent years reflects the life-prolonging benefit effects of ART.

As a result of the introduction of ART, the course of HIV infection has changed dramatically by prolonging the life of those on therapy. The life-prolonging effects of ART are also coupled with a decrease in both the incidence of opportunistic infections as well as AIDS-related deaths.[2] Furthermore, several studies have shown that the reduction of HIV viral load resulting from the use of ART is associated with reduction the of the HIV transmission in the population. [3-6]

The positive effects of ART are highly dependent on good adherence to treatment. A number of factors have been cited as being associated with compromised adherence to ART, but the evidence is conflicting on whether or not there is an association between socio-demographic factors and adherence behaviour. A number of studies have named depression/psychiatric illness, drug or alcohol use, non-disclosure of HIV infection and lack of social support as common predictors of non-adherence to ART.[7-10] The other factors associated with non-adherence are: treatment side effects; ART regimen complexity; the demands around medication and food timing caused by taking ART; inadequate knowledge and negative beliefs about HIV and effectiveness of ART.[11,12] Within this complex environment, adherence is vital and loss to follow-up (LTF) is a threat to successful ART programmes.

1.2 Background

South Africa is ranked first in the world in terms of the prevalence of HIV (19.1%).[13] It is therefore not surprising that the National Department of Health (NDOH) has named HIV/AIDS as one of its priorities and has committed itself to the combat of the disease, as well as to strengthening the effectiveness of the health system in order to be able to deal with this epidemic.[14] This commitment was evident when the South African President announced government's intentions of increasing the number of people on ART during his launch of the HIV Counselling and Testing (HCT) campaign in April 2010.[14]

The commitment by government is also evident in the National Strategic Plan (NSP) on HIV/AIDS, TB and STIs (20012 – 2016) which reflects one of government's goals of having at least 70% retention in ART programmes five years after initiation of ART.[15] Also reflected in the NSP, is the country's 20-year vision of "zero new TB and HIV infections, zero new infections due to vertical transmission, zero preventable deaths associated with HIV and TB and zero discrimination associated with HIV and TB".[15] It is therefore crucial that challenges such as LTF which may hinder progress towards the realisation of these goals are addressed.

The South African government has taken a number of positive strides towards achieving the goals and objectives and realising its vision as cited in the NSP. These include the development and implementation, over recent years, of policies in support of the multi-sectoral response to HIV such as the Department of Basic Education Integrated Strategy on HIV, STIs and TB; the National Framework for the implementation of Comprehensive HIV and AIDS Programmes for Offenders and Personnel; the National Action Plan for Orphans and Vulnerable Children and Promotion of Equality and Prevention of Unfair Discrimination. In addition to these policies, one of the largest HCT campaigns in the world was implemented in April 2010 which, according to reports, saw 13 million people being tested for HIV by the end of 2011. Also reported, was the reduction of antiretroviral therapy drug prices which made it possible for government to see an additional 650 000 people access

ART in 2011 bringing the total number of people on treatment to 1.6 million by the end of that financial year. In March 2011 the active case-finding programme for TB patients was launched which involves tracing family members of people diagnosed with TB so that they can be screened for TB and counselled for HIV testing, given the high TB-HIV co-morbidity in the country. A comprehensive Prevention of Mother-to-Child Transmission (PMTCT) of HIV programme was also implemented which has seen a dramatic increase in PMTCT coverage and a decline in the number of vertical transmissions of HIV.[16]

Another recently reported achievement by the health sector is the implementation of Medical Male Circumcision (MMC) at public health institutions as another means of reducing sexual transmission of HIV.

Despite the government's efforts to increase ART coverage, these efforts are negated by the high rate of LTF amongst patients on ART treatment programmes in the public sector.[17] LTF of patients on ART has negative implications on the adherence to treatment which is considered to be critical in the success of ART.[18] LTF also has negative financial implications in terms of the cost involved when patients who were previously LTF have to be re-started on treatment and the time spent by health care workers to re-initiate treatment. Adherence to ART is considered to be a critical health promotion behaviour for those on this form of treatment.[19] Clearly, it is essential to focus on finding ways of reducing LTF of those already on treatment or the government's goal of having 70% of those who have been started on treatment alive five years after initiation will not be achieved.[15] The effort of reducing LTF needs to involve determining the characteristics of those patients who have become LTF and how these compare to the rest of patient population in ART programmes. This information will enable those involved in the care of these patients early identification of those patients at risk to LTF.

1.3 Problem statement

Despite improvements in ensuring universal access to ART patient retention in ART programmes still remains a challenge.

Patient retention in ART programmes is crucial as the success of ART is highly dependent on good patient adherence to treatment. Constant clinical monitoring of patients on ART for drug adverse effects, clinical progress as well as adherence especially in the early stages of treatment are crucial activities of ART programmes.[20] Therefore, consistent attendance of scheduled follow-up visits by patients is important.

A number of studies of the extent of LTF in ART programmes have shown that LTF remains one of the challenges such programmes face.[20-26]Although the extent of LTF varies between different regions, the negative effects it has on adherence to treatment is the same.

LTF of patients in ART programmes makes it difficult to assess the overall performance of these interventions because it results in a significant number of patients for whom the clinical outcomes are not known. LTF also poses a risk to the very patients who have defaulted as they may be at risk of clinical deterioration, developing resistance to antiretroviral (ARV) drugs or death. LTF also has negative public health implications as studies have shown that the reduction of HIV viral load by ART is associated with the benefit of reduced HIV transmission risk.[3-6] Moreover, the development of drug resistance has negative public health implications as it will result in the spread of drug-resistant virus strains. These negative effects of LTF indicate the need to address this challenge in order to ensure that the positive effects of ART programmes are not negated.

1.4 Purpose of the study

LTF accounts for higher numbers of patient attrition compared to death in ART programmes.[26] However, patients who are LTF are at a higher risk of death due to interrupted monitoring and clinical care than those retained in care.[22,27]

Other previous researches which explored LTF have shown that this problem ranges from region to region, with the extent being anything between 3 – 45% within the first year after ART initiation. LTF is even higher in lower to medium income countries compared to the more affluent countries.[20-32]South Africa is a middle income country and the extent of the problem of LTF is comparable to that of other similar income countries. It has been noted that the efforts to increase ART coverage by the South African government in partnership with non-governmental organisations (NGOs), are negated by the high rate of loss to follow-up amongst patients on ART treatment programmes in the public sector.[17]

A variation in the level of patient retention exists amongst different ART programmes in the country with some being able to retain higher numbers of patients than others. There is therefore a need for those programmes with higher rates of LTF to understand factors associated with it. The programmes with higher rates of LTF need to be able to identify the characteristics of those patients who become lost in order to develop strategies of minimizing the problem and to learn from those programmes which have been able to retain a higher proportion of patients.[26]

The objectives of this study, by making use of data routinely collected at public ART clinics, was to determine the extent of LTF and examine patient characteristics associated with it so that strategies aimed at preventing the problem can be developed and implemented. This information will be useful to providers of care in ART programmes as it will help them to identify patients who are at risk promptly even before ART is initiated.

1.5 Research design and method

This is a retrospective cohort study that explores data that has been collected in the SOZO data base during routine services on patients with HIV for factors associated with LTF. The SOZO data base was introduced in 2007 under the President's Emergency Plan for AIDS Relief (PEPFAR) programme by the Foundation for Professional Development (FPD) and is used by basically most public health ARV clinics in the Tshwane district. The clinics are situated in urban, semi-urban and rural areas and provide free of cost services to the population in the respective catchment areas.

Records of patients 15 years and older who were initiated on ART between the 1st July and 31st December 2010 at eleven PEPFAR - supported public ART roll-out clinics was extracted from the SOZO data base. The data was cleaned and analysed. Analysis of the follow-up of these patients from the time of ART initiation was carried-out in order to determine if any were LTF within the first 12 months. The follow-up period studied ended on the 31st March 2012. The data was collected by healthcare workers at the participating primary healthcare clinics during routine follow-up of the patients.

The following criteria were used to select patient records for inclusion in the study:

Inclusion Criteria

- Patients who were at least 15 years or older and who were initiated on antiretroviral therapy and received care in the identified public sector ARV clinics between 1st July and 31st December 2010.

Exclusion Criteria

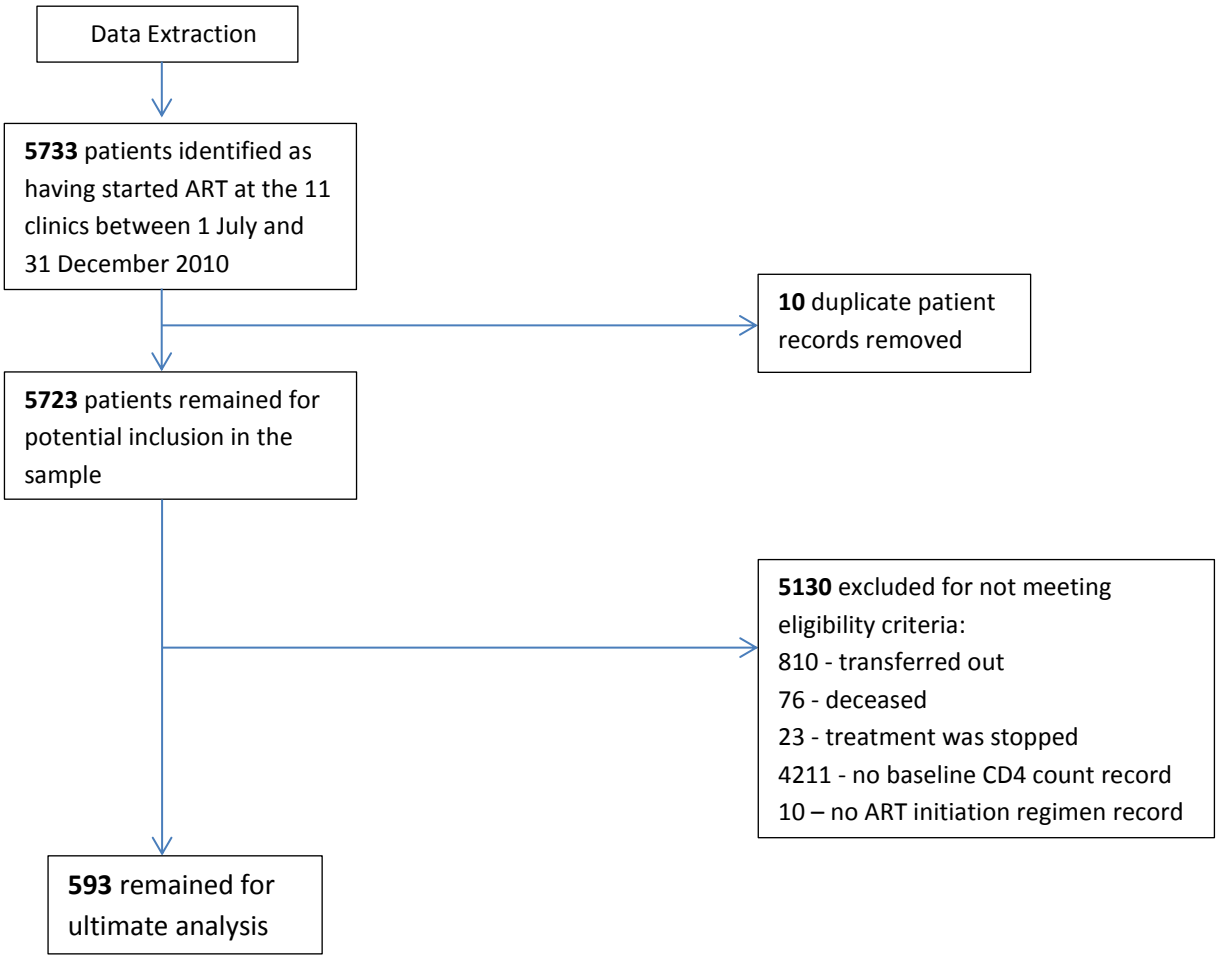
- Paediatric patients.
- Patients who were initiated on antiretroviral therapy solely for prevention of mother to child transmission of HIV.

- Patients who had been recorded as dead (as the definition of LTF in this study excluded those who were known to have died)
- Patients with a record of transfer to another clinic.
- Patients whose treatment was stopped by a healthcare worker for any reason.

From a total of 5723 patients who were identified to have been started on ART at these clinics between 1st July and 31st December 2010, records of 593 patients were found to be suitable for the analysis which was higher than the initial target of 300, considering that purposive sampling was conducted.

Cleaning of the data included the removal of duplication and any variables which were not of interest in this study (Figure 1).

Figure 1: Summary of data synthesis



1.6 Ethical Issues

Approval to conduct the analysis was granted by the Faculty of Health Sciences Ethics Committee of the University of Pretoria. Further permission for the review of patient records in the SOZO data base was granted by FPD (Appendix A & B).

Following extraction from the SOZO data base, the data was saved in a password-protected folder on the researcher's personal computer. The data will also be kept on a CD for a minimum of 15 years at University of Pretoria as per regulations which govern the conduct of clinical research in South Africa.

1.7 Summary

Part 1 of this mini-dissertation has introduced the context, research problem, study design and methods and the ethical issues of this research. Part 2 reports on the findings in the format of a journal article that is aimed at the BMC Public Health Journal. Part 3 outlines the limitations of this research, explores the health policy and management implications of the findings, highlights avenues for future research and concludes with some service delivery recommendations.

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PART 2

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2.2. JOURNAL ARTICLE

Characteristics of adult patients who are lost to follow-up in antiretroviral roll out clinics: a retrospective cohort study in Gauteng, South Africa

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ABSTRACT

Background

Notwithstanding South Africa's achievements in making antiretroviral treatment (ART) universally available and accessible, the HIV programme is known to be challenged by patients being lost to follow-up (LTF) after starting ART. It is critical to the success of the country's HIV programme to understand and address factors contributing to LTF. Electronic patient records have become standard in most ART clinics across South Africa and contain a large amount of demographic and clinical data that has been routinely collected predominantly for reporting purposes. The information from these data bases should allow drawing a detailed picture on treatment outcomes and predictive factors which may be of importance to improve ART services. This explorative study uses the SOZO data base, which at the time of the study hosted the data of 110 969 patients in 40 ART clinics around four provinces in South Africa, to determine the rate of patients being LTF within 12 months following ART initiation and to identify factors predicting LTF.

Methods

Electronic files of all 5723 patients who started ART between the 1st July and 31st December 2010 in the Tshwane district and were older than 15 years at ART start were considered for this retrospective cohort study. Only patients with information available on their date of birth, sex, marital status, CD4 count at baseline and prescribed ART regimen were included in the study. LTF was assessed for the 12 month period following ART initiation. Logistic regression analysis was used to identify the factors associated with LTF.

Results

Two hundred and thirty-seven (39.97%) of the 593 participants who met the inclusion criteria were found to have been LTF within the first 12 months of ART. The odds of being LTF during the first 12 months after starting ART was higher in participants 50 years or older compared to the other age groups (53.16% LTF; OR=1.44; p=0.003), in participants with a baseline CD4 cell count < 100 cells/mm^3 (43.4% LTF; OR= 1.42; p=0.064) and in participants initiated on an AZT or d4T containing regimen (51.61% LTF; OR=1.78; p=0.12 and 46.99% LTF; OR=1.48; p=0.1).

Conclusion

An LTF rate of 40% is unacceptably high. Strategies to minimise LTF need to focus on the young and elderly patients, patients with advanced HIV and those started on certain regimens.

Keywords

Loss to follow-up; Antiretroviral therapy; Human immune deficiency virus

Background

South Africa, is ranked first in the world in terms of the prevalence of HIV (19.1%).[1] It is therefore not surprising that the National Department of Health (NDOH) has named HIV/AIDS as one of its priorities and has committed itself to the combat of the disease, as well as to strengthening the effectiveness of the health system in order to be able to deal with this epidemic.[2] This commitment was evident when the South African President announced government's intentions of increasing the number of people on Antiretroviral Therapy (ART) during his launch of the HIV Counselling and Testing (HCT) campaign in April 2010.[2]

The commitment by government is also evident in the National Strategic Plan (NSP) on HIV/AIDS, TB and STIs (20012 – 2016) which reflects government's goals of initiating at least 80% of eligible patients on ART, with 70% alive and on treatment five years after initiation.[3]

The global commitment by governments throughout the world to providing universal access to ART in response to the crisis imposed by the HIV epidemic has also resulted in a large number of people living with the HIV globally. According to statistics provided by the World Health Organization (WHO), there were approximately 35 million people living with HIV (PLWHIV) in 2013.[4]The increase in

the number of PLWHIV observed in recent years reflects the life-prolonging benefit effects of ART.

As a result of the introduction of ART, the course of HIV infection has changed dramatically by prolonging the life of those on therapy. The life-prolonging effects of ART are also coupled with the decrease in the incidence of opportunistic infections and thus reducing the morbidity and mortality related to AIDS.[5]Several studies have shown that the reduction of HIV viral load resulting from the use of ART is also associated with the reduction of the rate of HIV transmission in the population.[6-9]

It is however crucial to ensure that patients who have been started on ART are retained in ART programmes in order for the positive effects of ART to be maintained. In South Africa it has been noted that despite the government's efforts to increase ART coverage, these efforts are negated by the high rate of loss to follow-up (LTF) amongst patients on ART treatment programmes in the public sector.[10] LTF of patients on ART has negative implications on the adherence to treatment which is considered to be critical in the success of ART.[11] LTF also has negative financial implications in terms of the cost involved when patients who were previously LTF have to be re-started on treatment and also the time spent by health care workers to re-initiate treatment. Adherence to ART is considered to be a critical health promotion behaviour for those on this form of treatment.[12] It is clear that it is essential to focus on finding strategies aimed at reducing LTF of those already on treatment or the government's goal of having 70% of those who have been started on treatment alive five years after initiation will not be achieved.[3] The effort of reducing LTF needs to involve determining the characteristics of those patients who have become lost to follow-up and how these compare to the rest of the patient population in ART programmes in order to enable early identification of other patients who are potentially at risk to LTF.

A number of studies have named depression/psychiatric illness, drug or alcohol use, non-disclosure of HIV infection and lack of social support as common predictors of

non-adherence to ART.[13-16] The other factors associated with non-adherence are treatment side effects; ART regimen complexity; the demands around medication and food timing caused by taking ART; inadequate knowledge and negative beliefs about HIV and the effectiveness of ART.[17,18] Within this complex environment, adherence is vital and LTF is a threat to successful ART programmes. While on the one hand, adherence is defined as the extent to which one follows the prescriber's recommendations when using prescribed medicine in terms of both timing and dosing,[19] LTF refers to the non-attendance of scheduled clinic visits for a given time period. As non-attendance can potentially result in adherence being compromised, it is crucial that strategies to reduce LTF are established.

Electronic patient records have become standard in most ART clinics across South Africa. These records contain a huge amount of demographic and clinical data which is routinely collected predominantly for reporting purposes. The information contained in these data bases can be a source of knowledge for a learning health care system.[20] This is a new approach to research which is inductive (which is about discovery, pattern recognition and generating new insight) as opposed to the deductive approach used in a clinical trial (which comes with a hypothesis and proves or disproves that hypothesis).[20] Through proper analysis of this data, a detailed picture on treatment outcomes such as LTF can be drawn which may be of importance to improve ART services.

This study uses these electronic records to identify and describe the characteristics of those patients who become LTF and compares this group with the population of patients who are retained in ART programmes at eleven public roll-out clinics in Gauteng, South Africa.

Methods

Study design

This is a retrospective cohort study that explores data that has been collected in the SOZO data base during routine services on patients with HIV for factors associated with LTF.

Setting

The SOZO data base in the study period included records of 110 969 patients in 40 Presidential Emergency Plan for AIDS Relief (PEPFAR)-supported public sector ARV clinics in Tshwane district and neighbouring districts in Mpumalanga, North West and Limpopo.[21] The SOZO data base was introduced in 2007 under the PEPFAR programme by the Foundation for Professional Development (FPD) and is used by the majority of public ARV clinics in the Tshwane district. The clinics are situated in urban, semi-urban and rural areas and provide free of cost services to the population in the respective catchment areas.

Study population

Only data files of participants who were 15 years or older and initiated on ART between the 1st July and the 31st December 2010 at the 11 PEPFAR-supported public sector ARV clinics in Tshwane district were included into this study and had to have the following information available: date of birth; ART initiation date; baseline CD4 cell count and ART regimen at initiation.

Patients who had been recorded as having died during the 12 months following initiation; patients who had had their treatment stopped by clinicians and patients with a record of transfer to another clinic were excluded from the analysis.

Measurements

Demographic and clinical data extracted from the data base included ART clinic identity; sex (categorised into either male or female); marital status (categorised into either married or single); baseline CD4 cell count (CD4 cell count results within 168 days prior to ART initiation); date of birth; date of ART initiation; age at ART initiation; date of clinic visits following ART initiation (up to and including 31st March 2012); and the ART regimen at initiation [classified according to their compliance with the SA National Treatment guidelines into "1st line" (TDF + 3TC/FTC + EFV/NVP;

D4T + 3TC/FTC + EFV/NVP and AZT +3TC/FTC + EFV/NVP), "2nd line" (TDF + 3TC/FTC + LPV/r and AZT + 3TC/FTC + LPV/r) and "other" regimen as well as into "yes" and "no" (based on whether or not they complied with the guidelines' 1st line and 2nd line regimens)].

Loss to follow-up

According to international standards[22], LTF was defined as having missed a scheduled clinic visit by 90 days or more. This study considered LTF during the first 12 months after starting ART only.

Data analysis

Data were analysed using Microsoft® Excel 2010 and STATA 12. Descriptive analysis included determining the total LTF rates and the LTF rates according to strata (age; sex; marital status; baseline CD4 cell count and ART regimen). Explorative analysis included bivariate and multivariate logistic regression in order to identify factors associated with LTF. Statistical significance was defined at a 95% level using Pearson's Chi square test. Variables showing an association at significance level of 0.05 were considered in multivariate logistic regression.

Ethical approval

Approval to conduct the analysis was granted by the Faculty of Health Sciences Ethics Committee of the University of Pretoria (Reference number 138/2013). Further permission to obtain and review patient records in the SOZO data base was granted by FPD.

Results

Out of 5723 patients who started ART between 1st July and 31st December 2010, 593 met the criteria for inclusion into the study. Five thousand one hundred and thirty patients who started ART during that period were excluded because: they had been recorded as having died within the 12 months following ART initiation (n = 76, 1.3%); had had their treatment stopped by clinicians (n = 23, 0.4%); had been transferred to another clinic (n = 810, 14%); had no record of baseline CD4 cell count results (n = 4211, 73.6%) or no record of information about the ART regimen they commenced on (n = 10, 0.2%). The final sample size of 593 was considered adequate as it was higher than the initial target of 300, considering that purposive sampling was conducted.

Sample characteristics

The participants that qualified for this study came from 11 clinics (Table 1). The majority of patients (88.9%) came from three clinics [Odi clinic (47.4%), Jubilee clinic (29.0%) and K.T. Matubatse clinic (12.5%)].

The mean age of the participants was 37.5 years (SD +/- 10.14) with those between 30 and 39 years accounting for more than 40% of the total number of participants. Two thirds of the participants were women. The majority of the participants (85.16%) were single. Eighty percent of the participants had a CD4 cell count which was less than 200 cells/mm^3 and 50% of these had a CD4 cell count below 100 cells/mm^3. Ninety-eight percent of patients were initiated on regimens which are in keeping with the SA National Guidelines and 95.45% of those patients were started on the first line regimen.[23]

Loss to follow-up

Overall, 237 (39.97%) study participants were found to have been LTF within the first 12 months after starting ART (Table 2).

The rates of participants' LTF differed significantly between the age groups. Participants over 50 years constituted the largest proportion of participants who were LTF at 12 months after ART initiation (53.2%) while only 34.4% of the participants between 30 and 39 years of age were LTF.

No significant differences in the LTF rates were found for sex or marital status. Similarly, no significant differences were seen when considering the CD4 cell count at baseline or whether the ART regimen the participant was started on was compliant with the national ART guidelines or whether a participant was started on a first or second line regimen.

With regards to the NRTI backbone chosen for the ART regimen this study found that the participants who started on an AZT or d4T containing regimen had higher rates of LTF than participants who commenced on a TDF based combination. These findings were statistically significant on a 90% ($p < 0.1$) level. However, no significant differences were seen when stratifying the regimen according to the third drug (EFV, NVP or a PI, respectively) chosen for the regimen.

Final logistic regression model for sample characteristics

The following variables were considered in the logistic regression model: age; sex; marital status; baseline CD4 count and ART regimen at initiation (Table 3). The odds of being LTF during the first 12 months of ART were higher for participants between 15 and 29 years of age (OR 1.44, $p = 0.091$) and, statistically significant, for participants 50 years or older (OR 2.16, $p = 0.003$) compared to participants between 30 and 39 years of age.

With regards to the CD4 cell count at baseline, the analysis revealed that participants with a CD4 cell count below 100 cells/mm^3 had higher odds and close to significance (OR 1.43, p = 0.064) of being LTF than those with a CD4 cell count above 100 and below 200 cells/mm^3.

Also participants with a d4T or AZT containing regimen appear to have higher odds of being LTF during the first 12 months of ART (OR 1.48 and OR 1.78, respectively). The findings however only reached a significance level of 90% (p = 0.10) and 88% (p = 0.12), respectively.

Neither sex nor marital status was found to be associated with LTF. The choice of the third drug (EFV, NVP or a PI) was also not predictive for LTF.

Discussion

This study investigated the extent of LTF at 12 months after being initiated on ART among the study population as well as the characteristics of those participants who were LTF.

This study found that 40% of patients reviewed were LTF during the first 12 months after initiation of ART. This rate of 40% LTF within the first 12 months of ART is comparable to those of other previous studies which reported rates as high as 45% within the said period.[24-30]A review of early loss of HIV patients on ART programmes in low-income countries revealed that LTF rate was related to the size of the ART programme as well as the method used to follow-up patients who had missed a clinic visit.[25] In that review it was found that programmes using passive follow-up methods and those with patients exceeding one thousand had markedly higher rates of LTF compared to programmes with smaller patient numbers and those using active follow-up methods.[25] The clinics reviewed in this study all had large ART programmes with passive patient follow-up methods.

A rate of LTF of a magnitude as high as that found in this study is unacceptable as it may limit the positive individual and population benefits of ART and can also act as an obstacle to the optimal monitoring and care of patients who are on ART.[29,31] LTF implies that patients who need to be on long-term treatment discontinue treatment which will most likely result in the deterioration of their immune status, rendering them prone to opportunistic infections. From an epidemiological point of view, this implies an increased risk of spread of HIV infection and the emergence of drug-resistant strains.

In order to prevent LTF it would be useful to know factors which are predictive of LTF. In order to assess these factors, this study therefore examined age at ART initiation, sex, marital status, CD4 cell count at ART initiation and the ART regimen participants were initiated on. The approach of this study was similar in part to a review of studies which looked at factors affecting adherence and had grouped the factors identified into demographic, therapy-related, social and economic, health system and disease factors.[32]

In terms of age, the findings show that participants over the age of 50 years (OR 2.16, p = 0.003) as well as participants younger than 30 years (OR 1.44, p = 0.091) were at a higher risk of being LTF at 12 months after starting ART compared to participants from 30 to 39 years of age. A South African study which explored reasons for LTF tracked down and interviewed patients who had been LTF and found that one of the reasons given by some of these patients was that they did not want to either disclose or seek permission fromtheir employers in order for them to be able to honour their follow-up appointments.[33] This reason could be a possible explanation for the higher odds of LTF in patients younger than 30 years in this study as the assumption would be that most in this age group would still either be at school/college or have just started new careers, The findings in participants older than 50 years are in agreement with findings of a study which reviewed LTF in a network of ART programmes in lower- income countries which also found older patients to be more prone to LTF compared to younger age groups.[25] The reasons for LTF in older patients may however be different to those in younger patients.

These reasons may include the fact that elderly patients may have other chronic co-morbidities which not only require more follow-up appointments but also these appoints could be at different clinics. This may have resulted in this group being unable to keep up or remember their multiple appointments. There is also a possibility that a small percentage of the elderly participants who were classified as having been LTF in this study may have actually died and this had not been recorded in their files – a likely outcome described by other studies that looked at outcomes of patients who had been classified as being LTF and which found that 20-60% of them had actually died.[31,34-41]

This study revealed that participants who had a CD4 cell count which was less than 100 cells/mm^3 were at higher risk of LTF at 12 months than participants with higher CD4 cell counts (OR 1.42, p = 0.064). This finding of higher risk of LTF in patients with lower CD4 cell counts is similar to that of another study.[25] Reasons for the higher risk of LTF in this category of participants could be due to various possibilities namely;: patients may have been too ill and weak to attend their clinic follow-up appointments; they may have discontinued ART because of additional and/or poorly tolerated treatment for co-morbidities or as a result of social hardships which are a consequence of advanced disease such as lack of income and transport money.

The results also indicated, at a lower risk significance level, that participants who were initiated on either d4T (OR 1.48, p = 0.102) or AZT (OR 1.78; p = 0.12) were found to be having a higher probability of LTF at 12 months compared to those who were initiated on TDF. To the best of the authors' knowledge, this is the first time this has been shown since the introduction of TDF as one of the drugs in the first line regimen in South Africa in 2010. Therapy-related factors are well known aspects for poor compliance and subsequently LTF.[32] The poor tolerability as well as toxicities associated with both AZT and d4T are likely reasons for this finding.[42-45] AZT is known to cause anaemia in some patients especially in the early stages of therapy and d4T has been associated with peripheral neuropathy; hyperlactetaemia and lactic acidosis as well as lipodystrophy. These results suggest that the replacement of d4T and AZT with TDF in the first-line regimen for adult patients in the South African public sector might have indeed been beneficial to the ART programme in

terms of mitigating LTF and improving adherence. In addition to the possible positive impact on the public programmes, these findings also highlight that special attention needs to be given to assure adherence to ART in those patients who have to be initiated on either a d4T or AZT containing regimen due to contra-indications of TDF (e.g. renal impairment).

In agreement with other studies, no association was found between LTF and gender in this study.[25,35] Similarly, no association was found between LTF and participants' marital status.

The findings of this study indicate the need to revise certain aspects of the provision of ART services in order to mitigate LTF in ART programmes. In terms of reducing LTF in young patients, changing clinic operation times to be patient-friendlier such as providing services in the evening or over weekends or having a medicine delivery system on those follow-ups which do not require clinical or laboratory assessment as well as workplace programmes could be useful. However these strategies would imply a major change in clinic operations and some may have cost implications.

Elderly patients as well as those patients in advanced stages of the disease could benefit from the integration of ART services into the rest of the other primary health care (PHC) services, decentralisation of ART services as well as community outreach programmes which can include among other things medicine delivery to those who are too ill or weak to go to health facilities. The NDOH has actually taken a number of important steps in terms of decentralisation of ART services with the implementation of the Nurse Initiated Management of Antiretroviral Therapy (NIMART) programme as well as the planned reengineering of PHC to include Ward Based Outreach Teams (WBOT). The national health department has also acknowledged the need to address the issue of integration of HIV, TB and PMTCT services in order to improve the retention of patients on treatment in care.[46]

This study used electronic data which had been collected routinely at public ART clinics. The inductive approach of this study is suitable to explore available data and to identify factors associated with LTF. The study however is limited by the data that is available in the SOZO data base. The biggest challenge is related to the quality of the data in the form of missing information about why a patient did not come back for follow-up. Under the current routine conditions, this information is very difficult to get as information on whether a patient has died, was hospitalised or has moved is only occasionally fed back into the system. This could have resulted in false high LTF rates as patients who might have actually died, moved or changed the clinic were erroneously attributed as "LTF". It is however believed that this percentage of misclassified patients is small and did not affect the essence of the findings of this study.

The information on whether a patient attended the clinic however is reliably captured. Once a patient comes to the clinic the receptionist will register the patient in the system, which automatically creates a date and time stamp.

However, another shortcoming when using the SOZO database for analytical purposes is that relevant clinical information is not captured in the data base. For example only 12% of the patients were found to have a baseline CD4 count captured in the system. This however, did affect patients in care and patients classified as LTF similarly, thus should not have impacted on the overall results of this study other than by reducing the statistical power of the findings.

Notwithstanding these challenges, electronic record systems have an enormous potential not only to facilitate reporting but also to generate information about patient populations that could be of tremendous value to inform clinical practice and service delivery. Efforts should therefore be made to improve data quality in order to tap this source.

Conclusion

Forty percent LTF during the first year after ART initiation is very high and poses a major challenge to the country's ART programme. One of the challenges with LTF is that it makes it difficult to evaluate the true impact of the implemented ART programmes as information of those who have been LTF is often missing in patient records. Younger and elderly patients, patients in advanced stages of HIV disease (CD4 cell count < 100) and patients who are started on d4T or AZT containing ART regimens are at high risk for LTF. It is crucial that strategies to improve patient retention be developed with these identified factors in mind. Measures that may positively impact the retention of patients on treatment include decentralisation of services (has already been implemented in the form of NIMART); community outreach programmes with active follow-up of patients who are LTF(there is currently a plan for PHC re-engineering which will include WBOT) and the provision of more flexible services at clinic level through extended opening hours especially for patients who are employed or have to attend school or through medicine delivery systems.

List of abbreviations

ART - Antiretroviral therapy

HIV – Human immunodeficiency virus

WHO – World Health Organisation

PLWHIV – People living with HIV

NDOH – National department of health

HCT – HIV counselling and testing

NSP – National strategic plan

TB - Tuberculosis

LTF – Loss to follow-up

PMTCT – Prevention of mother-to-child transmission

MMC – Medical male circumcision

PEPFAR – President's emergency plan for AIDS relief

FPD – Foundation for professional development

AZT - Zidovudine

3TC - Lamivudine

FTC - Emtricitabine

d4T - Stavudine

TDF- Tenofovir

ABC - Abacavir

EFV - Efavirenz

NVP - Nevirapine

LPV - Lopinavir

NRTI – Nucleoside reverse transcriptase inhibitor

NNRTI – Non-nucleoside reverse transcriptase inhibitor

PI – Protease inhibitor

PHC – Primary Health Care

NIMART – Nurse Initiated Management of Antiretroviral Treatment

WBOT – Ward based Outreach Teams

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TM participated in the design of the study, data extraction, cleaning, analysis and interpretation of the results. LW contributed in the design and review of the protocol. FK participated in data extraction and cleaning as well as providing advice on the analysis plan. All authors contributed to the final report and approved the final manuscript

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Tables

Table 1: Sample Characteristics

Characteristic	Category	n	%
Site			
	Cullinan	3	0.51
	Dark city	2	0.34
	Jubilee	172	29.01
	Kalafong	16	2.7
	K.T. Motubatse	74	12.48
	Laudium	29	4.89
	Odi	281	47.39
	Pretoria Academic	2	0.34
	Pretoria West	5	0.84
	Soshanguve	5	0.84
	Stanza Bopape	4	0.67
Age (years)			
	15 - 29	144	24.28
	30 - 39	244	41.15
	40 - 49	126	21.25
	>/=50	79	13.32
Mean Age	37.5 (SD 10.14)		
Sex			
	Female	397	66.95
	Male	196	33.05
Marital Status			
	Married	88	14.84
	Single	505	85.16
Baseline CD4 cell count (cells/mm)			
	<100	235	39.63
	100 - 199	242	40.81
	>/=200	116	19.56
Compliance with national ART guidelines			
	Yes	579	97.64
	No	14	2.36
ART regimen categories			
	1st line	566	95.45
	2nd line	12	2.02
	Other	15	2.53

NRTI backbone			
	TDF+3TC/FTC	470	80.48
	d4T+3TC/FTC	83	14.21
	AZT+3TC/FTC	31	5.31
NNRTI or PI containing regimen			
	NVP	99	16.92
	EFV	472	80.68
	LPV	14	2.4

Table 2: Loss to follow-up by sample characteristics

Variable (n)		On ART at 12months		LTF at 12 months		p-value*
		% (n)		% (n)		
	593	356	60.03	237	39.97	
Age (N=593)						
15 - 29	144	82	56.94	62	43.06	0.023
30 - 39	244	160	65.57	84	34.43	
40 - 49	126	77	61.11	49	38.89	
>/=50	79	37	46.84	42	53.16	
Sex						
Female	397	233	58.69	164	41.31	0.342
Male	196	123	62.76	73	37.24	
Marital status						
Married	88	52	59.09	36	40.91	0.845
Single	505	304	60.2	201	39.8	
Baseline CD4 cell count (cells/mm^3)						
<100	235	133	56.6	102	43.4	0.135
100 - 199	242	157	64.88	85	35.12	
>/=200	116	66	56.9	50	43.1	
Compliance with national ART guidelines						
Yes	579	350	60.45	229	39.55	0.184
No	14	6	42.86	8	57.14	

ART regimen categories						
1st line	566	340	60.07	226	39.93	0.295
2nd line	12	9	75	3	25	
NRTI backbone						
TDF+3TC/FTC	470	294	62.55	176	37.45	
d4T+3TC/FTC	83	44	53.01	39	46.99	0.096
AZT+3TC/FTC	31	15	48.39	16	51.61	
NNRTI or PI containing regimen						
NVP	99	57	57.58	42	42.42	
EFV	472	285	60.38	187	39.62	0.828
LPV	14	9	64.29	5	35.71	

*Pearson's chi square test

Table 3: Final logistic regression model for characteristics of patients LTF

Variable		Odds ratio (95% CI)	p-value
Age (years)			
	15 - 29	1.44 (0.94 - 2.19)	0.091
	30 - 39	1 (referent)	
	40 - 49	1.21 (0.77 - 1.89)	0.397
	>/=50	2.16 (1.29 - 3.61)	0.003
Sex			
	Male	1 (referent)	
	Female	1.18 (0.83 - 1.68)	0.342
Marital Status			
	Married	1 (referent)	
	Single	0.95 (0.60 - 1.51)	0.845
Baseline CD4 count (cells/mm^3)			
	<100	1.42 (0.98 - 2.04)	0.064
	100 - 199	1 (referent)	
	>/=200	1.39 (0.89 - 2.19)	0.145
NRTI backbone			
	TDF+3TC/FTC	1 (referent)	
	d4T+3TC/FTC	1.48 (0.93 - 2.37)	0.102
	AZT+3TC/FTC	1.78 (0.86 - 3.69)	0.12
NNRTI or PI containing regimen			
	NVP	1.33 (0.42 - 4.25)	0.634
	EFV	1.18 (0.39 - 3.58)	0.769
	LPV	1 (referent)	

PART 3

3.1 Policy implications

The proportion of patients who were found to be lost to follow-up (LTF) at 12 months after initiation of ART at the 11 clinics around Tshwane was 39.97% collectively. This level of LTF is far from the targeted 20% or less as recommended in the WHO HIVDR EWI.[1] These results indicate that a strategy needs to be developed in order to improve the level of LTF in these clinics so that the risk of transmission and acquisition of HIV which is resistant to currently recommended first line therapy can be minimised in these populations. These strategies could involve the development of a structured ways of tracing patients who miss their follow-up appointment especially in the first year after ART initiation in order to help improve retention. This tracing strategy could range from sending a SMS reminder of follow-up appointments via a cellular phone a few days before a scheduled appointment and even after a missed scheduled appointment. This strategy of sending reminders via SMS has been shown to be of benefit by one review of studies in health and informatics.[2]

The association found between age and LTF in this study with young adults (age group 15-29 years) and the elderly (older than 50 years) being more likely to be LTF indicates the need to explore age-specific patient retention strategies. These strategies could include scheduling follow-up visits on weekends for school or university students in order to accommodate those young adults who might not be able to come on week days because of fear of missing out on school activities. The re-introduction of school health outreach programmes through the proposed community oriented PHC re-engineering model could serve as another means to address and help minimise loss to follow-up of the younger patients who are still at schools or university/colleges as well as the elderly not only in ART programmes but also in other aspects of health.

Perhaps the decentralisation of ART services as well as their integration into the rest of the clinic services has tried to address the issue of clinic follow-up for multiple co-

morbidities which the elderly patient is often faced with. It would be interesting to see if the findings would be different if an analysis were to be conducted for patients initiated in the years after the implementation of this measure.

The possibility that some of the participants who had died could have been misclassified as having been LTF, could have contributed to the finding of an association between LTF at 12 months with very low baseline CD4 count. This finding highlights the importance of routine HIV testing to help identify infected individuals early. This issue may already have been addressed through the launch of HCT campaign in April 2010, which has since been transformed from campaign mode and incorporated into routine public health services.[3] Over 20 million people, had reportedly undergone HIV testing between the launch of HCT in April 2010 and the end of March 2012.[3] It would however be of benefit to see whether these numbers have translated into fewer individuals initiating ART at very low CD counts in the last couple of years, something which could not be observed from this study as the period of observation was too soon after the launch.

3.2 Topics for further research

In view of the large number of patients excluded in this analysis as a result of missing data and the variables (such as employment status and whether or not a patient had a treatment buddy or belonged to a support group at the time of initiation of ART) which were initially planned to be looked at but were dropped due to the information not being routinely collected, a prospective cohort study in which required data is collected would provide a more accurate picture of the extent of LTF at 12 months after ART.

Research on the effects of decentralising and integrating ART services into the rest of the other primary health care services on patient retention may provide valuable information for future policy.

Research on whether the implementation of HCT has had an effect in the reduction of individuals who initiate ART at advanced stages of the disease, something which

has been associated with higher risk of development of Immune Reconstitution Inflammatory Syndrome (IRIS) could also be useful.[4-7]

This study may have partially showed one of the benefits of the introduction in 2010 of TDF as one of the drugs used in first-line ART regimen for adults in South Africa as TDF was found to be associated with a far lesser risk of LTF compared to AZT and d4T. Therefore research into this subject may help the drivers of the national public health system in gauging the effects of the introduction of TDF on patients' clinical, immunological and virological outcomes.

3.3 Limitations of the study

The results for this study should be interpreted with the following limitations in mind:

- Only 12% of patients who were eligible for inclusion in the study could actually be considered due to the incomplete baseline CD4 count data and 1.7% of these were further eliminated due to lack of data on their ART regimen at initiation. This exclusion of certain patients could have introduced some selection bias. However, since the demographic characteristics of the two groups namely all those that had started ART in the identified months and the ones who were eventually included in the analysis as shown in Tables I & II were similar, the expectation is that this bias would be minimal.
- It is possible that some of the patients who have been classified as LTF in this analysis may have in actual fact self-transferred (without reporting to the site where they initiated treatment) to other clinics outside Tshwane which were not utilising the SOZO data system at the time of transfer.
- It is also possible that some patients may have died and this information may not have been made available to the clinics where they were started treatment. These patients would have been misclassified as LTF in this analysis.

3.4 Recommendations

The following points could assist in limiting the problem of LTF in ART programmes:

3.4.1 Developing strategies to assist patients in remembering their clinic appointment dates such as sending SMS reminders a few days prior to their appointment date.

3.4.2 Allocating staff to assist in tracing those patients who have missed their visits by more than seven days. This point supports the planned implementation of the community-orientated PHC model.

3.4.3 Integration of ART services into the rest of the PHC services in those clinics where this system has not already been implemented might help address the issue of multiple co-morbidities and the LTF among clinic population who are older than 50 years.

3.4.4 Intensification of pre-ART adherence counselling especially in those patients with the characteristics which have been identified as associated with LTF namely young adults and the elderly; patients with CD4 counts at initiation and those who are started on an AZT or d4T-containing ART regimen.

3.4.5 Developing ways to improve the quality of data contained in electronic record systems given the recognised potential such data has not only to facilitate reporting but also to generate information about patient populations that could be of tremendous value to inform clinical practice.

3.5 Conclusions

Results of this study show that LTF is still a challenge ART programmes face despite the tremendous progress made in ensuring universal access to ART. Development of strategies to reduce LTF is crucial if the goals of having 70% of those initiated on ART alive and still on treatment after five years of initiation is to be realised. Being aware of the characteristics of those patients who are likely to be LTF could play a major role in the development of strategies specifically aimed at minimising this challenge.

3.6 References

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Table I: Demographic characteristics of all patients started on ART

Characteristic		n	%
Age (years)			
	15 - 29	1 469	25.67
	30 - 39	2 339	40.87
	40 - 49	1 287	22.49
	>/=50	628	10.97
Mean Age	37.02 (SD 9.86)		
Sex			
	Female	3 867	67.57
	Male	1 856	32.43
Marital Status			
	Married	1 058	18.49
	Single	4 665	81.51

Table II: Demographic characteristics of patients included in analysis

Characteristic		n	%
Age (years)			
	15 - 29	144	24.28
	30 - 39	244	41.15
	40 - 49	126	21.25
	>/=50	79	13.32
Mean Age (years)	37.5 (SD 10.14)		
Sex			
	Female	397	66.95
	Male	196	33.05
Marital Status			
	Married	88	14.84
	Single	505	85.16

Appendix A

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.
- IRB 0000 2235 IORG0001762 Approved dd 13/04/2011 and Expires 13/04/2014.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

25/04/2013

Approval Notice
New Application

Ethics Reference No.: 138/2013

Title: Characteristics of adult patients who are lost to follow-up in antiretroviral roll out clinics – Gauteng, South Africa
Department: SHSPH; University of Pretoria.

Dear Thuthukile Molefe / Mrs Liz Wolvaardt

The **New Application** for your research received on the 4/04/2013, was approved by the Faculty of Health Sciences Research Ethics Committee on the 24/04/2013

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year, till the end of April 2014 .
- Please remember to use your protocol number (138/2013) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
Standard Conditions:
- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

Additional Conditions:
- The title is acceptable as is.

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

We wish you the best with your research.

Yours sincerely

Dr R Sommers; MBChB; MMed (Int); MPharMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

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Appendix B

FPD
www.foundation.co.za

28 March 2013

The Students' Ethics Committee
University of Pretoria

TO WHOM IT MAY CONCERN

GRANTING OF PERMISSION TO USE SOZO DATA IN A RESEARCH STUDY

The research proposal document: *Characteristics of adult patients who are lost to follow-up in antiretroviral treatment and to compare them with the population of patients on ART in twelve public roll-out clinics in Gauteng South Africa* by Thuthukile JE Molefe, currently studying MPH, has been reviewed by myself.

The objectives of the study are;

- *To determine the proportion of patients who become lost to follow-up at 12 months after initiation in antiretroviral therapy roll-out clinics in Gauteng, South Africa.*
- *To identify characteristics of those patients who become lost to follow-up at urban and rural antiretroviral therapy roll-out clinics.*
- *To compare the characteristics of patients who are lost to follow-up with those of patients who are not lost to follow-up.*

Permission is granted that the student may conduct the study using unlinked SOZO data at Laudium Community Health Centre, Odi Hospital, Tshwane District Hospital, Jubillee Hospital and Cullinan Rehabilitation Hospital, so long as District permissions are granted.

Regards

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