Introduction

South Africa has made tremendous progress in its response to the HIV epidemic. This includes the provision of HIV testing, linkage and retention in HIV care and treatment with antiretroviral therapy. The public sector HIV care and treatment programme is delivered through a mixture of health care facilities including primary care facilities and has grown from a few such facilities in 2004 to more than 3800 in 2015.\(^1\) By the end of 2015, the programme was testing an estimated 10 million people per year and there were 3.3 million people remaining on antiretroviral therapy (ART).\(^1,2\)

There have been concerns from many quarters that while there is good progress overall, males are lagging in terms of programme outcomes such as ART initiation, retention in care and mortality on or off ART. Although recent systematic reviews of global literature did not find significant differences between males and females with respect to CD4 count recovery and virological suppression or failure, they did find increased risk of mortality and progression to AIDS amongst males in low and middle income countries.\(^3,4\) Currently, South Africa faces a quadruple burden of diseases including communicable diseases such as tuberculosis (TB) and HIV, non-communicable diseases, perinatal and maternal diseases as well as injuries. The country also has high levels of alcohol and substance abuse which are more prevalent in males. All these factors may contribute to adverse outcomes amongst males receiving HIV care and treatment.

Against this backdrop a review of South African literature was conducted to determine the extent of gender disparities in HIV care and treatment and to identify factors associated with it. It is envisaged that the findings of this review will inform the design and implementation of interventions or surveillance activities within the national HIV care and treatment programme.

Methods

Search strategy

A keyword search in Google scholar was conducted using the following search terms “HIV testing”, “linkage”, “retention”, “CD4 count”, “viral suppression”, “mortality”, “gender” and “South Africa”. Google scholar was selected for convenience and also to improve yields from sources other than peer reviewed journals indexed in PubMed. The search was limited to publications from 1\(^{st}\) January 2010 until 30\(^{th}\) April 2016 and published in English. From the initial titles retrieved, a title screen was conducted in order to identify publications for abstract review. From the abstract review, publications for full text review were identified. For abstracts to be eligible for full text review, they had to report data on cohorts from which any of the following outcomes were measured: linkage to care, ART initiation of first line ART, CD4 count recovery or gain, retention in care, viral suppression, or mortality in adults aged 15 years or older by gender. If the outcomes were not reported by gender, there had to be evidence that the authors conducted adjusted analyses including gender which would permit extraction of data on relevant outcomes by
gender. If studies were multi-country, there had to be evidence that data from South Africa was reported separately.

**Data extraction and analysis**

From the full texts reviewed, studies which met the eligibility criteria for inclusion in the study were identified. From eligible studies, data on the following study characteristics were extracted: year of publication, location, description of study cohort (population, size, proportion of males, median age), outcomes measured and their definitions, study findings according to the outcomes and any other factors independently associated with the outcomes. If one paper described more than one eligible cohort, data on all eligible cohorts were extracted. Data were extracted and entered into an Excel [Microsoft ®, Seattle, Washington, USA] spreadsheet. Data from the spreadsheet were then exported into Stata® 14 [Stata Corporation, College Station, Texas] for analysis. Descriptive statistics were used to describe the studies according to study characteristics and outcomes. The study findings were summarised qualitatively and associated factors were described.

**Results**

From an initial 1540 titles retrieved, the first unique 601 titles (39%) were screened. From these titles, 120 abstracts were reviewed and 53 abstracts were identified for full text review. Following full text review of the 53 papers, 20 papers describing 23 cohorts were found to be eligible for inclusion in the review. The most common reasons for exclusion of papers at the full text review were outcomes not being reported by gender [14 (43.7%)] and studies reporting irrelevant outcomes [10 (34.4%)].

**Description of studies**

Of the 20 studies included in the review, more than half were published prior to 2013. Most studies reported data collected in three provinces – Gauteng, KwaZulu-Natal and Western Cape with only three studies including other provinces. The median proportion of males in the cohorts was 35% (range 11.1- 54%), the median of median ages reported was 35 years (range 31- 38 years) while the median of the median CD4 counts at ART initiation was 101 cells/µl (range 81- 132 cells/µl). Median duration of follow up was reported by 11 of the 20 studies and ranged from 0.8 – 3 years. The most common outcomes reported in the studies were mortality (n=12), retention (loss to follow up or default, n=7) and CD4 gains/ response to ART (n=5). For source information and summary details of each study, please contact Dr Tendesayi Kufa-Chakezha at TendesayiKC@nicd.ac.za.

**Summary of findings**

1. **Mortality**

The mortality rates reported for women ranged between 3.4 - 11.8 per 100 person-years while that for males ranged between 5.1 – 20.3 per 100 person-years. For eight of the 12 studies in which gender was independently associated with mortality, males were 11-40% more likely to die during ART. Other factors which were independently associated with increased mortality were CD4 counts < 100 cells/µl at start of ART, current CD4 counts <100 cells/µl, late WHO stage at ART start, anaemia, low BMI and lack of virological suppression. Two studies showed that although mortality decreased with increasing duration on ART, the gender disparity in mortality increased with increasing duration on ART. One study examined the ratios of female: male mortality by age amongst HIV-positive individuals on ART and compared them to the same ratios amongst HIV negative individuals and found that the gender disparities in mortality were less among the HIV positive individuals compared to the HIV negative individuals, suggesting that higher non-HIV mortality in males on
Art compared to females on ART may also contribute to this gender disparity in mortality.

2. Loss to follow-up or default
The proportion of females who were lost to follow-up or defaulted from ART using study specific definitions ranged from 9.8% - 21.6% compared to 11.8- 27.9% amongst males. In five of the seven studies in which gender was independently associated with loss to follow-up or default, males were 18- 51% more likely to be lost to follow-up or to default from ART compared to females. Other factors associated with increased default or loss to follow up were lower CD4 counts at ART start (although one study found an association of loss to follow up with higher CD4 counts), younger age and increasing calendar years.

3. Viral suppression or virological failure
Three studies reported on virological suppression or virological failure. From these studies males were 20-36% less likely to be virally suppressed but were no more likely than females to develop virological failure. Other factors independently associated with lack of viral suppression were younger age, lower CD4 counts and use of nevirapine based regimens.

4. CD4 count gains
In four of five studies which reported on CD4 count gains, females were more likely to have statistically significant higher CD4 count increases after adjusting for other covariates. The fifth study reported no differences in the proportions of males and females with CD4 counts < 200 cells/µl at the start of ART who still had CD4 counts < 200cells/µl after 12 months in spite of being virally suppressed.

5. Linkage to care and ART initiation
Three studies reported on linkage to care and ART initiation in four cohorts and all showed trends towards females being more likely to initiate ART in the defined time periods compared to males, although the differences were not statistically significant in two cohorts.

Discussion and conclusions
The review of studies from South Africa revealed that males in HIV care and treatment are more likely to start ART late, are less likely to be virally suppressed or retained in care and are more likely to die in the follow-up period after ART initiation after adjusting for pre-treatment factors and, in a few studies, most recent CD4 counts and viral loads. These studies also reported on other factors independently associated with adverse outcomes including low CD4 counts, lack of viral suppression and duration on treatment. Most of the studies did not provide reasons for these gender disparities but discussed possible biological and socio-behavioural factors which could not be adequately adjusted or controlled for in the analyses.

It is likely that there are multiple factors which may account for gender disparities in HIV care and treatment. One factor may be the age at which males acquired HIV infection and subsequently started ART. From the 2012 Human Sciences Research Council (HSRC) survey, HIV incidence peaked in the 15-24 year age group amongst females compared to the 25-49 year age group amongst males. This age gap in HIV acquisition likely translates into an even wider age gap at the initiation of ART, taking into account late ART initiation by males. Older age at ART initiation is independently associated with mortality and sub-optimal response to ART in the presence of viral suppression. Other factors suggested in recent reviews and studies include: biological differences in innate immunity; differences in dietary practices with males more likely to experience micronutrient deficiencies linked to the immune response to HIV;
higher likelihood of males experiencing internalised stigma within the health system and therefore less likely to seek care timeously; higher likelihood that younger, single and unemployed males struggle to initiate ART and remain on treatment.\textsuperscript{7,10,11}

This review was limited to data from South African cohorts in order to maximise the generalizability of findings to the country’s HIV positive populations. However, the review had some limitations. Firstly, this was not an exhaustive systematic review and may have missed studies reporting contrary findings. Studies identified in this limited review included most of the large treatment cohorts in the country and it is unlikely that any missed studies would have found results that are very different from those reported here. Another limitation was that the studies used different definitions of the outcomes. Because the review was not attempting to calculate summary estimates for the outcomes but rather summarise the effect sizes and their directions, the studies were still useful despite this limitation. A further limitation was that the studies had limited durations of follow-up ranging from just under one year to three years. Findings on outcomes such as mortality and virological suppression or failure may look different at longer durations of follow-up.

The findings from this semi-systematic review suggest that more interventions to improve the early uptake of HIV testing, ART initiation, adherence to treatment and retention in care amongst males need to be evaluated. These interventions may include extending clinic opening hours to after-hours or weekends to cater for working populations, decongesting clinics to reduce clinic waiting times and use of peer support.\textsuperscript{12,13} From a surveillance perspective, these gender disparities show that it is imperative to record and report gender-specific data and to develop gender-specific HIV care cascades in evaluating progress towards the 90-90-90 targets. Further research into the modifiable factors which account for these gender disparities are also needed and the contribution of non-HIV causes to morbidity and mortality among people on ART is also needed.

References


