Can highly active antiretroviral therapy reduce the spread of HIV?: A study in a township of South Africa.

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Running head: HAART and the spread of HIV

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SUMMARY

Background Calls have been made for the large-scale delivery of highly active antiretroviral therapy (HAART) to people infected with HIV in developing countries. If this is to be done, estimates of the number of people who currently require HAART in high HIV-prevalence areas of sub-Saharan Africa are needed and the impact of the widespread use of HAART on transmission and hence the spread of HIV must be assessed.

Objectives To estimate the proportion of people who would be eligible for combination antiretroviral (ARV) therapy and hence to evaluate the potential impact of providing HAART on the spread of HIV-1 under the WHO guideline, in a South African township with a high prevalence of HIV-1.

Design A community-based, cross-sectional study in a township near Johannesburg, South Africa of a random sample of approximately 1,000 men and women aged 15 to 49 years.

Materials and methods Background characteristics and sexual behaviour were recorded by questionnaire. Participants were tested for HIV-1 and their CD4+ cell counts and plasma HIV-1 RNA loads were measured. The proportion of people whose CD4+ cell count was less than 200 cells/mm^3 and would be eligible to receive HAART under the WHO guideline was estimated. The potential impact of antiretroviral drugs on the spread of HIV-1 in this setting was determined firstly by estimating among the partnerships engaged in by HIV-1 positive individuals the proportion of spousal and non-spousal partnerships eligible to receive HAART, and secondly by calculating the potential impact of HAART on the annual risk of HIV-1 transmission due to sexual contacts of HIV-1 infected persons. The results were compared with those obtained when using the USDHHS guideline.

Results The overall prevalence of HIV-1 infection was 21.8% (19.2% – 24.6%), and of these people 9.5% (6.1% – 14.9%), or 2.1% (1.3% – 3.3%) of all 15 to 49 year olds, would be eligible for HAART (ranges are 95% confidence limits). In each of the next three years 6.3% (4.6% – 8.4%) of those currently infected with HIV-1 will need to start HAART. Among the partnerships where individuals were HIV-1 positive only a small proportion of spousal partnerships (7.6%; 3.4% – 15.6%) and non-spousal partnerships (5.7%; 3.0% – 10.2%) involve a partner with a CD4+ cell count below 200 cells/mm^3 and would benefit from the reduction of transmission due to the

decrease in plasma HIV-1 RNA load under HAART. Estimates of the impact of HAART on the annual risk of HIV-1 transmission show that this risk would be reduced by 11.9% (7.1% – 17.0%). When using USDHHS guideline the fraction of HIV-1 positive eligible for HAART reached 56.3% (49.1% – 63.2%) and the impact of HAART on the annual risk of HIV-1 transmission reached 71.8% (64.5% – 77.5%).

Conclusion The population impact of HAART on reducing sexual transmission of HIV-1 is likely to be small under the WHO guideline and reducing the spread of HIV-1 will depend on further strengthening conventional prevention efforts. A much higher impact of HAART is to be expected if USDHHS guideline is to be used.

Keywords: HAART, HIV, South Africa, CD4+, viral load, transmission.

INTRODUCTION

Sub-Saharan Africa remains the region most severely affected by HIV/AIDS. Approximately 3.4 million new infections occurred in 2001, bringing the total number of people living with HIV/AIDS in this region to 28.1 million. In South Africa, the prevalence of HIV-1 infection is among the highest in the world, with almost one-in-nine South Africans living with HIV/AIDS [1].

In developed countries, striking improvements have been reported in the health status and life expectancy of HIV-infected patients, as a result of the widespread use of antiretroviral therapy [2-10]. However, 90% of people infected with HIV live in the developing world while only 4% of those who need antiretroviral treatment currently have access to the drugs they require [11]. Several studies have evaluated the feasibility of delivering antiretroviral therapy (ART) to patients in resource-limited settings [12, 13], but despite international pressure to implement highly active antiretroviral therapy (HAART) in such countries, treatment requirements have yet to be precisely characterised. In developing countries with high HIV prevalence, such as South Africa, the fraction of the population who would be eligible for HAART under the World health Organisation (WHO) guideline [11] is not precisely known. It is not also known how this fraction will change if the United States Department of Health and Human Services (USDHHS) guideline [14] is used. Such information is needed to calculate the cost of scaling up antiretroviral treatments and to prepare health systems to deliver these treatments. In addition, the potential impact of the widespread use of antiretroviral drugs on the spread of HIV remains unclear and requires evaluation. There are biological and epidemiological reasons to believe that antiretroviral therapy will reduce sexual transmission of HIV. Biological studies have shown that antiretroviral drugs decrease HIV in seminal fluid [15] and in cervicovaginal secretions [16]. An epidemiological study of discordant couples has shown that the use of zidovudine by infected men was associated with a 50% reduction in the risk of transmission of HIV to their female sexual partner [17], suggesting that the wide use of HAART would slow down the spread of HIV in the countries where the route of transmission is mainly heterosexual.

The objectives of this study are firstly to estimate the proportion of the population who need HAART in a township in South Africa under the WHO guideline, secondly to estimate the short-term impact of providing anti-retroviral therapy on the spread of HIV and lastly to assess the impact of using the USDHHS guideline on these estimations.

MATERIALS AND METHODS

Survey

In April 2002, a population-based, cross-sectional study was conducted in a township 40 kilometres south of Johannesburg, South Africa. Households were selected by a two-stage random sampling technique. Index houses were randomly selected from a map obtained from the local municipal offices. Using each index house as a starting point, a cluster of households was identified by starting to the right of the index house and counting households around the street block and adjacent street blocks until 50 households had been reached. A self-weighting random sample of 20 households was then chosen from each cluster. All men and women aged 15 to 49 years, who slept in the selected households the night before the study team's visit, were eligible for inclusion in the study. The consent form was presented in the language of the respondent, who was invited to take part in the study, and those who agreed were asked to sign the consent form. The response rate was 68%. Eligible participants were transported to a local facility for the interviews and the collection of blood and urine samples. If eligible participants were not at home, the study team made up to three repeat visits on different days at different times. The fieldwork was done in the late afternoon, when residents returned from work, to reach as many residents as possible. Fieldwork was conducted on Monday to Thursday and again on Saturdays to ensure that people who work during the week could be reached. Where it was not possible for participants to go directly to the interviewing points, or for household members who were not home, appointments were made at times suited to the participants and these appointments were followed up.

The questionnaire used in this study was based on a UNAIDS questionnaire [18]. The interviewers completed the questionnaire during a private interview in the preferred language of the interviewee. Data were collected on background and behavioural characteristics. Sexual partners were divided into spousal and non-spousal partners. The spousal partners were partners to whom the respondents were married or lived with as married. The non-spousal partners were all the other partners. The questionnaire allowed for a detailed description of all the non-spousal partners of the last twelve months, including those with whom the respondent had only one sexual contact. In addition, specific questions were asked about the use of condoms in the last months with non-spousal partners.

During the survey, participants with symptoms of sexually transmitted infections (STIs) were encouraged to go to the local STI clinic for treatment. Participants who wished to know their HIV status were offered a separate free ELISA test with pre- and post-test counselling to be arranged through the normal clinical channels. Blood samples were tested for syphilis, HIV-1, CD4+ count and plasma HIV-1 RNA load. Urine samples were tested for chlamydial infection.

When results were available, a trained nurse delivered the syphilis and chlamydia infection test results directly to the participants. Participants with positive STI results were encouraged to seek treatment at the local STI clinics. Individuals with fewer than 200 CD4+ cells/mm^3 were

included in a specific programme that involved voluntary counselling and testing, prevention of opportunistic infections and access to ARV therapy. Pregnant women were informed of the possibility of reducing the mother-to-child transmission (MTCT) of HIV-1 during pregnancy and childbearing. The cost of transportation to health facilities where the MTCT programme was available free of charge was carried by the study.

Laboratory procedures

Following the interview, trained nurses collected whole blood and urine (first flow) samples. The urine samples were stored at 4°C and then transported the next day to the laboratory where they were stored at −70°C before being analysed. Two EDTA blood tubes of 20 ml of venous blood were taken and transported at room temperature to the laboratory on the following morning. One tube was centrifuged at 400 *g* for 10 minutes and 5 aliquots of plasma were then taken and frozen at −70° C. The second tube of blood was used to determine the CD4+ count.

An ELISA screen (Genscreen HIV1/2 version 2, Bio-Rad, France and Wellcozyme HIV recombinant, Abbot Murex, Dartford, UK) and ELISA confirmation (Vironostika HIV Uni-Formm II plus O, bioMerieux, Boxtel, Netherlands) were carried out on plasma to test for HIV-1 infection. Plasma HIV-1 RNA load was determined by reverse-transcription PCR using an assay designed to detect all M-group subtypes (Amplicor HIV-1 Monitor Test V1.5, Roche Diagnostic System Ins., Branchburg, New Jersey, USA) [19].

CD4+ cell counts were determined by BD FACSOUNT analysis, BD Biosciences, Belgium.

Syphilis testing was performed using a rapid plasma reagin (RPR) screen (Macro-Vue RPR Card Tests, Becton Dickinson Microbiology Systems, Becton Dickinson, Maryland) followed by a Fluorescent Treponemal Antibody Absorption (FTA-ABS) confirmatory test (FTA-ABS Test Sorbent, bioMérieux, France). A positive RPR (at any titre) and FTA-ABS were taken as evidence of recently acquired and/or untreated syphilis. Urine samples were tested for chlamydia infection using a qualitative DNA amplification method (Amplicor CT/NG Test, Roche Diagnostics, New Jersey, USA).

Ethics Ethical clearance was obtained from University of Witwatersrand Committee for Research on Human Subjects on the 8 February 2002 (protocol study n° M020103).

Data management

Laboratory results and data generated from questionnaires were entered twice into a database (Microsoft Access, Redmond, Washington, USA) by different people. The two entries were

compared and discrepancies were corrected. The data were then checked for inconsistencies. The files were then imported into the Statistical Package for Social Sciences (SPSS 8.0 for Windows, Chicago, Illinois, USA) and prepared for statistical analysis.

Statistical methods

Estimation and statistical tests

The Clopper-Pearson method, which is known to produce slightly conservative two-sided confidence intervals [20], was used to estimate confidence limits of proportions. (Unless otherwise stated ranges give 95% confidence limits.) Medians of quantitative data were calculated with their inter-quartile range (IQR). Quantitative data were compared between sub-groups using the Kruskal-Wallis test. The correlation between plasma HIV-1 RNA load and CD4+ count was analysed using the non-parametric Spearman correlation coefficient and by regression of $\log_{10}$ of the plasma HIV-1 RNA load against the CD4+ count.

Estimation of the proportion of the population who needs HAART under the WHO guideline

The current WHO recommendations are that all patients with CD4+ counts below 200 cells/mm^3 should be offered antiretroviral therapy [11] and we used this criterion to estimated the proportion of the 15- to 49-year-old population who currently required HAART. To conservatively estimate the proportion who will need to start HAART in the next three years, we assumed that the CD4+ cell counts decline by an average 50 cells/mm^3/year in untreated infected subjects [21-24]. As a result the fraction of the 15- to 49-year-old population who would need to start HAART in the next three years under WHO guideline was determined by the fraction of the sample with CD4+ counts in the range 201 – 350 cells/mm^3.

Estimation of the impact of HAART on the short-term spread of HIV-1 under the WHO guideline

Assuming that all people with CD4+ cell counts less than 200/mm^3 receive HAART, we used two approaches to estimate the short-term impact of providing HAART on the spread of HIV-1. The first approach assumes that any HIV-1-positive person receiving HAART will become less infectious. We thus calculated among partnerships engaged in by HIV-1 positive individuals the proportion of spousal and non-spousal partnerships eligible to receive HAART and, as a consequence, the transmission of HIV-1 could be reduced by HAART. In the second approach, we use data on the annual risk of HIV-1 transmission as a function of plasma HIV-1 RNA load from a study in Uganda [25] to estimate the potential number of new HIV-1 infections per year per HIV-1-infected person. From this we estimate the relative decrease in the annual risk of HIV-1 transmission assuming that HAART reduces plasma HIV-1 RNA load to fewer than 400 copies/ml. This approach allows for the contribution to the spread of HIV-1 by individuals with low CD4+ counts who are more likely to have high plasma HIV-1 RNA loads.

Impact of using the USDHHS guideline

To assess the impact of using the USDHHS guideline on the proportion of the population who require HAART, we recalculated this fraction using the USDHHS guideline which recommends initiation of HAART with CD4+ counts below 350 cells/mm^3 or plasma HIV-1 RNA load above 55,000 copies/ml [14]. Estimation of the impact of HAART on the short-term spread of HIV-1 under the USDHHS guideline was calculated as described above.

RESULTS

Background characteristics and sexual behaviour

Most households have electricity (89.0%, 85.8% – 91.6%) and piped water (88.2%, 84.9% – 90.8%) but flush toilets are less common (31.2%, 27.2% – 35.6%). The median (IQR) of the combined monthly income per household is 884 South African Rands (500 – 1500) corresponding to about 88 (50 – 150) Euros. The median (IQR) number of persons per household is 4 (3 – 5) and the median (IQR) number of persons per room is 1.4 (1 – 2).

A total of 930 people agreed to participate in the survey. The male-to-female ratio was 1:1.12. Background characteristics of the sample are given in table 1. At the time of the interview 90.9% (88.8% – 92.6%) of all participants reported having ever had sex. Among those who had experienced sexual intercourse, 34.7% (31.5% – 38.0%) said that they had never used a condom. Among men and women who had experienced sexual intercourse, 68.7% (63.8% – 73.2%) and 48.6% (43.9% – 53.3%), respectively, reported having had at least one non-spousal sexual partner in the last twelve months. Among men and women who were married or living as married, the corresponding figures were 32.6% (24.9% – 41.3%) and 11.7% (7.8% – 17.0%), respectively. Among those who had had sex in the last month with non-spousal partners, 39.2% (33.5 – 45.3%) reported that they always used condoms.

Prevalence of HIV-1, syphilis and chlamydial infections

The overall prevalence of HIV-1 infection was 21.8% (19.2% – 24.6%), 17.4% (14.1% – 21.4%) among men and 25.7% (21.9% – 30.0%) among women. The highest prevalence of HIV-1 by age was 34.4% (19.2% – 53.2%) among men aged 35 to 39 years and 46.4% (34.4% – 58.7%) among women aged 25 to 29 years. The median age of HIV-1-infected people was 31 (IQR 26 – 37) years for men, and 23 (IQR 19 – 32) years for women. Among those having a spousal and those having a non-spousal partnership, the prevalence of HIV-1 was 25.6% (21.1% – 30.7%) and 23.8% (20.1% – 27.9%), respectively. The prevalence of syphilis was 3.2% (1.9% – 5.4%) for men and 9.6% (7.4% – 12.8%) for women. The prevalence of chlamydia was 6.2% (4.3% – 8.9%) for men and 6.9% (5.0% – 9.6%) for women.

Distribution of plasma HIV-1 RNA load

The median (IQR) plasma HIV-1 RNA load was 55,750 (10,750 – 172,000) copies/ml [4.7 (4.0 – 5.2) copies/ml – log10], and the difference between men and women was not significantly different (Kruskal-Wallis test, $p = 0.59$). The median (IQR) plasma HIV-1 RNA load in participants with CD4+ counts less than 200 cells/mm^3 was 160,000 (72,900 – 410,000) copies/ml ml [5.2 (4.9 – 5.6) copies/ml – log10], and in participants with CD4+ counts higher than 200 cells/mm^3 it was

significantly lower at 46,800 (9,407 – 149,500) copies/ml [4.7 (4.0 – 5.2) copies/ml – log10], (Kruskal-Wallis test, $p = 0.000$).

Distribution of CD4+ counts

The median (IQR) CD4+ cell counts in the HIV-1-negative and -positive participants was 1,128 (911 – 1,371) cells/mm^3 and 475 (321 – 735) cells/mm^3, respectively, and the difference was statistically significant (Kruskal-Wallis test, $p = 0.000$). Among HIV-1-negative men, the median (IQR) CD4+ cell counts were 1,057 (850 – 1,316) cells/mm^3 and among women were slightly higher at 1,180 (963 – 1,436) cells/mm^3 (Kruskal-Wallis Test, $p = 0.000$). Among HIV-1-positive participants, the median CD4+ counts was 488 (321 – 740) cells/mm^3 and not statistically different between men and women (Kruskal-Wallis Test, $p = 0.17$). The distribution of CD4+ cell counts in HIV-1-infected individuals is given in figure 1.

Characteristics of HIV-1-infected subjects eligible for ARV therapy under the WHO guideline

Taking a CD4+ cell count of 200 cells/mm^3 as the critical level for the initiation of HAART, 9.5% (6.1% – 14.9%) of HIV-1-infected people, or 2.1% (1.3% – 3.3%) of 15- to 49-year-old, should be provided with HAART. The median age of these people was 33 (IQR, 26 – 36) years, with a male-to-female ratio of 1:2.2. 36.8% (20.4% – 73.9%) were married, and 47.4% (25.2% – 70.5%) reported at least one non-spousal sexual partner in the last twelve months.

At the time of the study, 18.9% (13.8% – 25.2%) of HIV-1-infected people had CD4+ cell counts between 200 and 349 cells/mm^3 so that 6.3% (4.6% – 8.4%) of those currently infected with HIV-1, or 1.4% (0.97% – 1.9%) of 15- to 49-year-olds, should start HAART in each of the next three years.

On average, plasma HIV-1 RNA load in copies/ml – log10 falls by a factor of 1.43 (1.32 – 1.56) for each 100 cells/mm^3 decline in CD4+ count, as shown in Figure 2. However, there is substantial dispersion in the data and a high proportion of individuals have a high plasma HIV-1 RNA load even though their CD4+ cell count is above 200 cells/mm^3.

Impact of HAART on the short-term spread of HIV-1 under the WHO guideline

Among spousal partnerships involving HIV-1-positive individuals, 7.6% (3.4% – 15.6%) had a CD4+ cell count below 200 cells/mm^3. Of the non-spousal partnerships in the last twelve months involving HIV-1-positive individuals, 5.7% (3.0% – 10.2%) had a CD4+ cell count below 200 cells/mm^3. Of the spousal and non-spousal partnerships in the last twelve months engaged in by HIV-1-positive individuals, a total of 6.3% (3.8% – 9.6%) had a CD4+ cell count below 200 cells/mm^3

The plasma HIV-1 RNA load stratified by CD4+ cell count is given in table 2. Combining the survey data from the present study with data on the annual risk of infection from a study in Uganda [26], we are able to estimate the probability that one current infection will give rise to a secondary infection in one year (annual risk of HIV-1 transmission). By assuming that those who receive HAART cease to be infectious, we also show in Table 2 that the provision of HAART to all infected subjects with a CD4+ cell count below 200 cells/mm^3 will reduce the annual risk of HIV-1 transmission by 11.9% (7.1% – 17.0%).

Impact of using the USDHHS guideline

If HAART were given to individuals with a CD4+ cell count below 350 cells/mm^3 or a plasma HIV-1 RNA load over 55,000 copies/ml, more people would need HAART and the impact on the short-term spread of HIV-1 would be greater. If this were done, we estimate (data not shown) that 56.3% (49.1% – 63.2%) of people infected with HIV-1 would have required HAART at the time of the study. As a result, 50.0% (39.5% – 60.5%) of spousal and 59.3% (52.0% – 66.2%) of non-spousal partnerships would potentially benefit from the resulting reduction of transmission, and the annual risk of HIV-1 transmission would be reduced by 71.8% (64.5% – 77.5%).

DISCUSSION

Number of people who need HAART

Marked improvements have been reported in the health status and life expectancy of HIV-1-infected individuals and coincide with the widespread use of antiretroviral drugs [2-10]. It is estimated that only 230,000 HIV-infected people in poor and middle-income countries are currently being treated with antiretroviral therapy and half of these are in Brazil. In Sub-Saharan Africa, where 70% of the HIV-1-infected people live, almost no or limited triple-combination HIV-1 treatment is used [24]. Several studies have investigated the feasibility and efficacy of anti-retroviral therapy in resource-poor settings and confirm that antiretroviral drugs can be successfully provided in developing countries [12, 13]. However, treatment requirements have not been well characterised in sub-Saharan countries. The current community-based study was conducted in a South African township of the Gauteng province with a very high prevalence of HIV-1. In this community the prevalence of HIV and syphilis among women that we found (9.6% and 25.7% respectively) was comparable to the prevalence (31.6% and 6.0% respectively) reported for the same province in the antenatal survey conducted in 2002 by the South African National Department of Health [27]. We estimate that 9.5% of all adults infected with HIV-1, or 2.1% of those aged 15 to

49 years, would be eligible for antiretroviral drugs, under the WHO guideline that recommends initiating HAART at CD4+ counts less than 200 cells/mm^3.

In addition, a further 6.3% of all adults infected with HIV-1, or 1.4% of those aged 15 to 49, should start HAART each year. Because HAART will reduce mortality, the number of individuals who need HAART will increase. As data on HAART coverage and on survival of patients receiving HAART in Africa become available it will be possible to estimate more precisely the demand for HAART and the cost of providing it [28, 29]. While the empirical data provided by this study represent an important first step, detailed public health and economic studies of the feasibility of testing and treating these individuals will allow for a precise estimate of the feasibility and cost of scaling up ARV therapy in settings with a high HIV prevalence. Such studies will make it possible to refine recent studies that have attempted to estimate the real cost of an effective response to the global AIDS epidemic [30, 31].

Estimates of the fraction of the population that need HAART in sub-Saharan Africa depend on the natural history of the epidemic and in particular its magnitude and maturity. Because the epidemic in South Africa has developed recently but very rapidly [1, 32], this study should be repeated in other sub-Saharan African settings, especially in countries where the prevalence is lower and where the epidemic is more mature and even declining. Nevertheless, it is unlikely that the proportion of HIV-positive people that need HAART will be dramatically different in other places in sub-Saharan Africa where the epidemic is driven primarily by heterosexual contact. HIV-1 has the same impact on the immune system, and the epidemic has probably reached an endemic state even in more recently affected countries.

When using the USDHHS guideline we found that a high proportion (more than 50%) of people infected with HIV-1 would have needed HAART at the time of the study. The drastic difference found when using the WHO and the USDHHS guideline is due to the strong difference in our HIV positive population between the fraction having CD4+ counts below 200 cells/mm^3(about 10%) and the fraction having a viral load above 55 000 copies/ml (about 50%). This indicates that the proportion of people who need HAART critically depends on the choice of guideline to be used. A recent study conducted in the Rakai population in Uganda found that 20% of infected persons had viral loads above 55 000 copies/ml and therefore need to receive HAART under the USDHHS guideline [33]. The reasons for such a difference when compared with our study are unclear. It could be due to the difference in the sample collection. Viral loads were determined from recently sampled plasma in our study and from archived serum in the Rakai study and such variation in the collection and the storage can at least partly explain the difference between the two studies [34]. It can also be due to the population sample. We have designed a specific cross-sectional approach for our study compared to the cohort used in the Rakai study.

Potential impact of HAART on the spread of HIV

The impact that HAART might have on the spread of HIV by reducing the infectivity of treated subjects and preventing subsequent sexual transmission remains unclear [35]. A mathematical model suggested that the widespread use of antiretroviral drugs could curb the HIV epidemic in a gay community in San Francisco [36]. A recently published stochastic simulation showed that in Uganda using the USDHHS guideline HAART will have a limited impact on the spread of HIV [33]. Here we have used two indicators to evaluate the short-term impact of the widespread use of HAART on HIV-1 transmission in a South African township where the prevalence of HIV-1 is high. The first indicator revealed that only a small proportion of spousal partnerships (7.6%) and non-spousal partnerships (5.7%) formed by HIV-1-infected individuals will potentially benefit from the likely reduction of transmission due to the decrease in plasma HIV-1 RNA load induced by HAART. The second indicator suggests that the annual risk of HIV-1 transmission would be reduced by 11.9%. The low numerical values of the two indicators show that the impact of HAART on the spread of HIV, by reducing the infectivity of treated subjects and preventing subsequent sexual transmission, will be small under the WHO guideline.

The first indicator takes into account the sexual activity of HIV-1 positive people in estimating the impact of HAART on the spread of HIV-1. Nevertheless, this indicator does not take into account that a proportion of the partnerships of HIV-1 positive individuals both partners could be HIV-1 positive. Therefore, this indicator is likely to be an overestimation of the proportion of sexual relationships that would benefit from the reduction of transmission due to the decrease in plasma HIV-1 RNA load by HAART. The second indicator was based on a study conducted in Uganda because of the lack of South African data on the relationship between HIV-1 viral load and sexual transmission of HIV-1. Therefore we cannot exclude that the result could have been slightly different if such data were available.

Because the average plasma HIV-1 RNA load only increases slowly as CD4+ count falls, the infectiousness of individuals who are eligible for HAART is close to the infectiousness of those who are not. As a result we can estimate the impact of HAART on the spread of HIV-1, as a first approximation, by the proportion of HIV-1-positive people who would receive HAART. This is confirmed by this study where 9.5% of HIV-1-infected people need HAART and the reduction in transmission was estimated to be 11.9%.

Many people will not be eligible for HAART because their CD4+ counts are above 200 cells/mm^3 even though they have a high plasma HIV-1 RNA load, and they will continue to contribute substantially to the spread of HIV after the introduction of HAART. In addition, individuals who are in the early asymptomatic period and have a negative HIV test, that is those who are newly infected or primary HIV-1-infected individuals, are not taken into account in the

current study and it is believed that they contribute substantially to the spread of HIV because of their high plasma HIV-1 RNA load [37]. However, this group is likely to be small because the window period of the ELISA HIV test used here is short.

Our estimation of the impact of HAART on the spread of HIV has been calculated assuming full coverage and that HAART reduces plasma HIV-1 RNA load to < 400 copies/ml. Because we used a relationship between plasma HIV-1 RNA load and HIV transmission [25] in which no transmission occurs with such low value of viral load, our hypothesis is equivalent to assuming that HAART completely suppresses infectiousness. It seems likely therefore that the estimation given in this study is an overestimation for at least three reasons. Firstly, it is unlikely that all eligible people infected with HIV will receive HAART for cultural and practical reasons. Secondly, studies conducted in Africa have pointed out the problems of non-adherence and drug resistance among treated patients [38-44]. Thirdly, it is unlikely that HIV-infected individuals receiving HAART will be completely uninfectious. Indeed, in HIV-1-infected men who are successfully receiving highly active antiretroviral therapy the virus may still be present in seminal cells and transmitted sexually [45], and it has been shown that treating HIV-1-infected men with zidovudine reduces, but does not eliminate, heterosexual transmission of HIV [17]. Finally, despite effective anti-retroviral therapy, high seminal plasma HIV-1 RNA loads occur during gonococcal urethritis [46] and patients may still be infected as evidenced by continued shedding of cells harbouring the HIV provirus [47].

When using the USDHHS guideline we found that the annual risk of HIV-1 transmission would be substantially reduced by more than two thirds. The drastic difference found when using the WHO and the USDHHS guideline is due to the marked difference in the populations eligible for HAART under the two guidelines. This indicates that the choice of guideline to be used in a developing country is of critical importance on the potential impact of antiretroviral therapy on the heterosexual spread of HIV. The aim of these guidelines is to recommend the point during the course of HIV infection at which antiretroviral therapy should be initiated but this point remains uncertain [48]. A consequence of our study is that the design of a guideline for developing countries has serious public health implications that should be taken into consideration. The relatively small impact of HAART when using the USDHHS guideline that was found in Uganda is in contrast with what was found in our study. The difference is likely the result of the lower proportion of HIV positive persons eligible for HAART in the Rakai population (about 20%) in comparison to the proportion in the South African population of this study (about 50%).

Consequences for prevention

Under the WHO guideline the limited effect of even the widespread use of HAART on the spread of HIV in sub-Saharan Africa found in this study suggests that HAART will not substantially reduce the heterosexual spread of HIV. Scaling up HAART should not lead to any relaxation in

prevention efforts to reduce the spread of HIV. In particular, we advocate, as others have [49], that the budget allocated for prevention should not be in competition with the budget allocated to treatment and should not be reduced. In this context the prevention of HIV infection should be based on established, cost-effective prevention strategies such as condom distribution, blood and injection safety measures, treatment of STIs, and changes of sexual behaviour [50].

In the population under study here, the prevalences of both syphilis and chlamydia are high, sexual risk behaviour is common and condom use is not optimal in non-spousal partnerships, although it is higher than in some other cities of sub-Saharan Africa [51-53]. This situation, characterised by low condom use, high rates of curable STIs and sexual risk behaviour is common in sub-Saharan Africa and prevention efforts to reduce the spread of HIV need to be substantially strengthened.

The development of HAART represents a major advance in the fight against HIV/AIDS and even though HAART has to be administered by trained health workers in health centres satisfying the minimum requirements for the delivery of such drugs [11], there is no doubt that HAART, which is already available in some countries in sub-Saharan Africa such as Senegal [42], will soon become available in other countries. The consequences of the availability of HAART on prevention are difficult to predict. HAART could facilitate HIV prevention. The targeted availability of an effective therapy could lead to an increase in demand for HIV testing and counselling, which has been shown to be effective in reducing risky sexual behaviours in heterosexual couples [35, 54], and to a lessening of the stigma associated with AIDS [13]. But HAART could also have a negative impact on prevention as recent studies in San Francisco and Amsterdam have provided evidence of an increase in unprotected sex among men who have sex with men, possibly due to the availability of HAART [11, 55, 56]. Detailed studies conducted in sub-Saharan Africa on the impact on prevention of the widespread use of HAART will be needed to judge adequately the complementary approaches of prevention and treatment of the HIV/AIDS epidemic in sub-Saharan communities highly infected by HIV.

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Figure

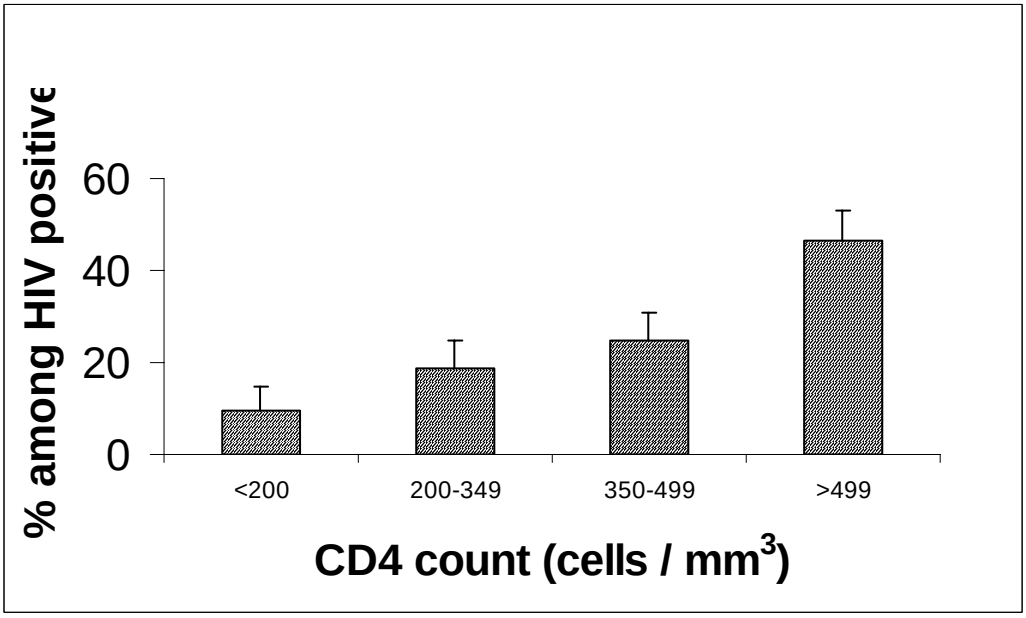

Figure 1. Distribution of CD4+ cell count among HIV-1-infected persons (with the upper limit of the 95% confidence interval).

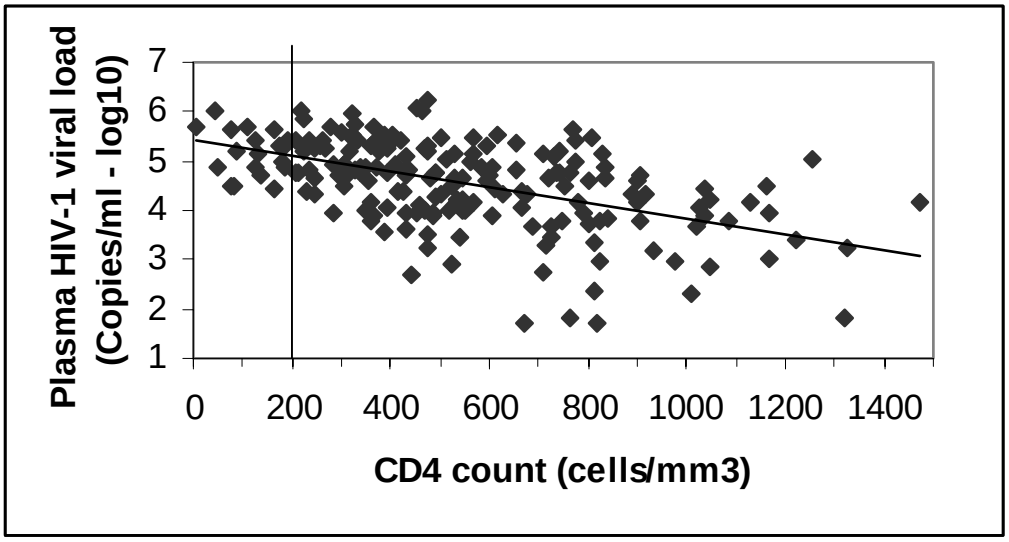

Figure 2. Plasma HIV-1 RNA load by CD4+ count among HIV-1-positive individuals. The regression line is plasma HIV-1 RNA load (copies/ml – log10) = 5.40 – 1.57 10^{-3} CD4+ count (Spearman's $\rho = -0.53$, $p = 0.000$).

Table 1. Background characteristics of men and women included in the survey.

	Men **N = 438**	**Women** **N = 492**	**Total** **N = 930**
Median age (IQR) years	25 (19 – 33)	28 (20 – 37)	26 (20 – 35)
Ethnic group (% in each category)			
Sotho	33.8	36.6	35.3
Tswana	7.5	6.5	7.0
Xhosa	9.6	13.0	11.4
Zulu	36.8	35.4	36.0
Other	12.3	8.5	10.3
Primary school completed (%)	84.5	83.3	83.9
Occupation (% in each category)			
Employed	37.4	25.0	30.9
Student	29.9	22.2	25.8
Unemployed	27.6	50.2	39.6
Other	5.0	2.6	3.8
Marital status (%)			
Married or living as married	30.8	41.9	36.7
Single	69.2	58.1	63.3

N: overall number of men and women in the analysis.

Table 2. Estimates of the potential impact of HAART on the annual risk of HIV-1 transmission. The table gives estimates of the annual risk of HIV-1 transmission as a function of plasma HIV-1 RNA load [27], the proportion of the present population falling into each plasma HIV-1 RNA load band, the weighted annual risk of HIV-1 transmission, the proportion of the population that will not receive HAART under present guidelines, and the weighted annual risk of HIV-1 transmission with the provision of HAART. The decrease in the annual risk of HIV-1 transmission from 0.171/person/yr without HAART to 0.151/person/year with HAART corresponds to a reduction of 11.9% (7.1% – 17.0%).

						Total (6)
Plasma HIV-1 RNA load (copies/ml)	< 399	400 – 3,499	3,500 – 9,999	10,000 – 49,999	>49,999	NA
Annual risk of HIV-1 transmission (/person/year)	0	0.04	0.12	0.14	0.23	NA
Percentage of HIV-1-positive population (%)	3.1 (1.1 – 6.5)	8.2 (4.7 – 12.9)	12.2 (8.0 – 17.7)	25.5 (19.6 – 32.2)	51.1 (43.8 – 58.2)	100
Weighted annual risk of HIV-1 transmission without HAART (/person/year)	0	0.00327 (0.00188 – 0.00516)	0.0147 (0.00960 – 0.0212)	0.0357 (0.0274 – 0.0451)	0.118 (0.101 – 0.134)	0.171 (0.1591 – 0.183)
Percentage of HIV-1-positive population with CD4+ counts > 200 cells/mm^3	3.1 (1.1 – 6.5)	8.2 (4.7 – 12.9)	12.2 (8.0 – 17.7)	23.5 (17.5 – 30.0)	43.4 (36.3 – 50.6)	90.3 (85.3 – 94.1)
Weighted annual risk of HIV-1 transmission with HAART (/person/year)	0	0.00327 (0.00188 – 0.00516)	0.0147 (0.00960 – 0.0212)	0.0329 (0.0245 – 0.0420)	0.0997 (0.0835 – 0.116)	0.151 (0.136 – 0.165)