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Incidence and prevalence of Type 2 diabetes mellitus with HIV infection in Africa: A systematic review and meta analysis

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ABSTRACT

Objectives: This systematic review aims to investigate the incidence and prevalence of diabetes in HIV infected patients in African populations. **Setting:** Only studies reporting data from Africa were included. **Participants:** A systematic search was conducted using four databases for articles referring to HIV infection and antiretroviral therapy, and type 2 diabetes mellitus in Africa. Articles were excluded if they reported data on children, animals or type 1 diabetes exclusively. **Main outcome measures:** Incidence of diabetes and prevalence of diabetes. Risk ratios were generated for pooled data using random effects models. Bias was assessed using an adapted Cochrane Collaboration bias assessment tool. **Results:** Of 1056 references that were screened, only 21 were selected for inclusion. Eight reported the incidence of diabetes in HIV infected patients, eight reported the prevalence of diabetes in HIV infected vs uninfected individuals, and five reported prevalence of diabetes in HIV treated vs untreated patients. Incidence rates ranged from -0.006 to 0.059 person years. Meta-analysis showed no significant differences between diabetes prevalence in HIV infected vs uninfected individuals (RR=1.612, 95% CI=0.616-4.205, p=0.329), or between HIV treated vs untreated patients (RR=1.380, 95% CI=0.663-2.872, p=0.389). Heterogeneity was high in both analyses (I2=87% and 52% respectively). **Conclusion:** Meta-analysis showed no association between diabetes prevalence and HIV infection or ART, however these results are limited by the high heterogeneity of the included studies and moderate to high risk of bias, as well as, the small number of studies included. There is a need for well designed prospective longitudinal studies with larger population sizes to better assess incidence and prevalence of type 2 diabetes in African patients with HIV. Furthermore, screening for diabetes using gold standard methods in this population is necessary. **Trial Registration:** PROSPERO: 42016038689.

KEYWORDS

Type 2 diabetes, HIV, Africa, combination antiretroviral therapy, incidence, prevalence

STRENGTHS AND LIMITATIONS OF THE STUDY

- This is the first systematic review of the literature examining associations between HIV infection and treatment with diabetes incidence and prevalence in Africa.
- The stringent inclusion criteria used is a strength of this systematic review.
- Differences in methods of diabetes diagnosis across studies is a limitation.
- Heterogeneity and moderate to high risk of bias across studies is a limitation.
- The small number of studies meeting the inclusion criteria is a limitation.

BACKGROUND

The introduction of combination antiretroviral therapies (cARTs) in the treatment of HIV infection has resulted in significant extension of the predicted lifespan of HIV infected patients1. Consequently, patients with HIV are potentially at greater risk of developing non-communicable diseases (NCDs) than due to ageing alone as the disease itself2, and treatments used to combat HIV, are associated with metabolic complications3.

Type 2 diabetes mellitus is one such disease that is becoming increasingly common, specifically in Africa due to rapidly transitioning lifestyles. An estimated 12.1 million people were living with diabetes in Africa in 20104 and it is predicted that this will increase to 23.9 milllion by 2030. Besides associations with age, obesity, sex, and race5; recent studies have associated diabetes with HIV infection, and with cART1, 3, 5. The mechanisms underlying these associations are not fully elucidated, but may reflect chronic systemic inflammation in response to HIV infection despite treatment6, 7, antiretroviral drug-induced mitochondrial dysfunction, lipodystrophy and comorbidities5. Diabetes is associated with increased morbidity and mortality, an estimated 1.5 million deaths were attributed directly to diabetes in 20128, and the implications of HIV infection and treatment on the incidence of diabetes is therefore important to explore. The aim of this systematic review is to investigate the incidence of diabetes in HIV infected patients in Africa, as well as, the prevalence of diabetes in HIV infected and cART treated patients in comparison to non infected and non treated individuals.

METHODS

The systematic review focused on the associations between HIV infection, ARV therapy and diabetes mellitus. This review was registered in the PROSPERO registry for systematic reviews (Registration number 42016038689)9, and was conducted in accordance with the PRISMA guidelines10.

Search Strategy

The search for this systematic review was conducted in May 2016 and included terms in the determinants of HIV infection and antiretroviral therapy, the domain of Africa, and the outcome of diabetes. Restrictions included age (adolescent or older), date of publication (after January 01 2008). The title and abstracts of articles in Pubmed, Scopus, the Cochrane library, and Embase were searched.

Study Selection

All intervention studies and observational studies (cohort, case-control, and cross-sectional) that assessed the relationship between HIV seropositivity with or without cART therapy, and diabetes in Africa were included. Animal studies, biomolecular studies, studies not written in English or French, case reports,

secondary analyses, and unpublished reports of proceedings were excluded. Studies reporting outcomes in children or pregnant women, or reporting type 1 diabetes outcomes only, or not reporting diabetes incidence or prevalence (but hyperglycemia or impaired glucose tolerance for example) were also excluded. Studies that did not report prevalence of diabetes in HIV infected compared to HIV uninfected participants; or prevalence of diabetes between cART exposure compared to untreated HIV infected patients; or incidence of diabetes in HIV infected patients were excluded. Authors of individual studies defined the criteria for diabetes diagnoses, and variant criteria were included provided diagnosis was made using a recognised score for a fasted blood glucose, or an oral glucose tolerance test (OGTT), or HbA1c values11.

Screening and data extraction

Two independent reviewers (AP, RJM) independently screened all articles retrieved by the search strategy by title and abstract for eligibility according to inclusion and exclusion criteria. Any discrepancies between the two reviewers were discussed and consensus was reached. The full text was accessed if necessary for further clarification. Full texts of eligible articles were then retrieved and divided amongst all reviewers. If no full text was available, one attempt was made to contact the author. Each full text was assessed for eligibility by one reviewer, and a second reviewer was available for consultation. Data extraction was then performed using a standardised data extraction form. One reviewer (AP) reassessed data extraction for all eligible full texts. Data of interest was study design, study setting and country, population, age, body mass index (BMI), number of patients included in each group, control population, cART treatment at the time of inclusion, duration of cART treatment, method of diabetes diagnosis, incidence of known risk factors for diabetes such as obesity, treatment provided for diabetes, incidence of diabetes in the control group and group with HIV and/or antiretroviral therapy, when applicable OR/RR, and follow-up duration. In cases of incomplete data, one attempt was made to contact the corresponding author by email and if no response was received the paper was excluded.

Data synthesis

Three separate analyses were performed for articles which examined incidence of diabetes; prevalence of diabetes in HIV infected vs uninfected participants; and prevalence of diabetes in HIV infected and treated vs untreated participants. Meta-analysis was conducted for articles with sufficiently homogenous outcome measures and study designs. The principle summary measure used was risk ratio (RR), and in cases of significant heterogeneity (I2>50%) a random effects model was applied. Analyses were conducted using OpenMetaAnalyst. Drawing upon the Cochrane Handbook for Systematic Reviews12, subgroup analyses would only be feasible when then are more than 10 studies

Risk of bias assessment

The Cochrane Collaboration's risk of bias tool was adapted for observational study design13. Studies were assessed as 'low risk', 'high risk', 'unclear risk', or 'not applicable' for the categories of completeness of data, origin of data, clarity of outcome definitions, consideration of confounders, blinding of researcher or clinician, and selection of study participants where applicable. For the 'confounders' category, data on the risk factors for diabetes of age, sex, and BMI were considered. The articles were assigned 'high risk' if none of these risk factors were controlled for and 'unclear risk' if some, but not all, were considered.

RESULTS

The search provided 1056 results. After screening, 21 articles met the eligibility criteria14-34 and were included in the analysis (Figure 1). Of these, 8[14-21] articles reported incidence of diabetes in HIV infected participants, 8[22-29] reported prevalence of diabetes in HIV infected participants compared to uninfected controls, and 5[30-34] reported prevalence of diabetes in HIV infected participants on treatment compared to untreated controls. In included studies, diabetes was diagnosed if participants were being treated for diabetes, or by oral glucose tolerance test (OGTT). As summarised in Table 1, four main criteria were used: World Health Organisation (WHO), American Diabetes Association (ADA), International Diabetes Federation (IDF), and National Cholesterol Education Programme (NCEP) criteria.

Table 1. Overview of diagnostic criteria used in the included studies

Criteria used	Definitions
WHO	Fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl).
ADA	Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) or 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during OGTT (75g) or A1C ≥6.5% (48 mmol/mol) or Random plasma glucose ≥200 mg/dL (11.1 mmol/L)
NCEP cut offs	Fasting plasma glucose ≥5.6 mmol/L
IDF	FPG ≥ 100 mg/dl (5.6 mmol/L)

WHO – world health organisation, ADA – American diabetes association, OGTT – oral glucose tolerance test, A1C - NCEP - National Cholesterol Education Programme, IDF – International diabetes federation

Risk of bias

A summary of the risk of bias assessment is presented in Figure 5. All included studies were observational, and 15 (71%) were case control studies. Almost half (42.9%) of the included studies had an unclear risk of bias due to confounding, and 61.2% of the included studies had a high risk of bias due to lack of blinding of researcher or clinician to case or control. In 86% of the included studies, diabetes was not the primary outcome. Three (14%) included studies were published conference proceedings.

Incidence of diabetes in HIV infected participants

Eight studies reported diabetes incidence in HIV infected participants (n=57160; Table 2). Incidence of diabetes was reported as absolute incidence, cumulative incidence, incidence proportion, and incidence rate in person years. Incidence rates ranged from -0.00617 to 0.059 person years16. The combined incidence rate for all the included studies over 92127 person years of follow up was 0.0165. One of the included studies compared incidence in treated vs untreated participants21, and another compared incidence in infected vs uninfected participants16. The rest of the studies assessed incidence in HIV infected and treated participants with no control group. Most participants were on cART, except for participants in the Sagna et al study who were on first line therapy, which was not clearly specified18. Mean age of participants ranged from 33.514 to 46 years17 (age was not stated by Magula et al16). Mean BMI ranged from 19.219 to 27.9 kg/m^{2}14, and was not stated in three of the studies16-18. Mean duration of follow up ranged from 1.56 years15 to 9 years17, and the total number of participants followed up to completion was n=57117. The majority of participants were female in all studies where sex was stated.

Table 2: Incidence Data

Author, Year	Setting	Population	Case	Control	ART	Follow up Mean/median	Diagnosis of diabetes	Prevalence at Baseline n(%)	Incidence at follow-up n(%)	Cumulative Incidence	Incidence Proportion	Incidence Rate (person years)	p-value
Abrahams, 2015	South Africa	103 women Mean age =33.5 Mean BMI=27.9	NA	NA	Stavudine/lamivudine	5.5 years n=94	ADA criteria	1 (1.0)	7 (7.5)	6.5%	5.83%	0.011	0.070
Diouf, 2014	Senegal	242 participants, 57% female mean age=46	NA	NA	Combinations including Lamivudine, Zidovudine, Stavudine, Indinavir, or Lopinavir	9 years n=242	WHO criteria, or prescription of anti-diabetic medication	48(20)	35(14)	-6%	-5.37%	-0.006	Not reported
George, 2009	South Africa	42 black participants, 65% female mean age=34.4 mean BMI=22.7	NA	NA	Stavudine/Zidovudine	2 years n=42	NCEP cut off	1(2.4)	1(2.5)	0.1%	0.001 %	0.005	>0.05
Karamchand, 2016	South Africa	56298 participants, 64% female Mean age=38.14 Mean BMI=25.95	NA	NA	First line NNRTI regimen containing efavirenz or nevirapine	1.56 years n=56298	Prescription of anti-diabetic medication	0(0)	1500 (2.66)	2.66%	2.66%	0.013	Not reported
Magula,	South	238	n=150	n=88	Initiated -	2 years	WHO	0(0)	13(8.66)	8.66%	8.66%	0.059	Not

2014	Africa	participants	treated	uninfected	tenofovir, lamivu- dine, efavirenz/nevirapine	n=150	criteria						reported
Ndona, 2012	DRC	102 participants, 51% female, mean age= 43.4 mean BMI=23.1	n=49 HIV+ treated	n=53 HIV+ untreated	stavudine + lamivudine, zidovudine + lamivudine + nevirapine, or efavirenz	4 years n=102	WHO criteria	Not stated	5(4.9)	4.9%	4.9%	0.01	0.06
Sagna, 2013	Burkino Faso	144 participants, Mean age=37	NA	NA	Not stated (first line therapy)	3 years n=128	Not stated	Not stated	3(2.3)	2.3%	2.1%	0.007	Not reported
Zannou, 2009	Benin	79 participants, 59.5% female mean age= 38 mean BMI=19.2	NA	NA	All started combination therapy. Lamivudine + stavudine +efavirenz	2 years n=61	WHO criteria	0(0)	6(7.6)	7.6%	7.6%	0.004	Not reported

ART – anti retro-viral therapy, BMI – Body mass index, OGTT – oral glucose tolerance test, ADA – American Diabetes Association, NNRTI – non nucleotide reverse transcriptase inhibitors, WHO – world health organization, NCEP – National Cholesterol Education Programme, DRC – Democratic Republic of Congo, HIV – Human immunodeficiency virus

Prevalence of diabetes in HIV infected compared to uninfected participants

A meta-analysis of eight studies comparing HIV infected (n=1715) to uninfected participants (n=2853) (Table 3) using a random effects model (I=84.79%) indicated no significant association between HIV infection and diabetes prevalence (RR=1.612, 95% CI=0.616- 4.205, p=0.329), Figure 3. The majority of included participants were female, except for the study conducted by Brand et al25, who only included males, and by Becker et al24, where the majority of participants were male. In four of the included studies, infected participants were not on treatment24-26, 28 and in a further two22, 23, treatment was not stated. The remaining two studies examined participants on cART. Mean age ranged from 20.622 to 62 years25 in uninfected participants and 21.122 to 47 years25 in infected participants. Age was significantly different between the case and control groups in three studies24, 25, 27. Mean BMI ranged from 20.622 to 28.1 kg/m^2 26 in uninfected participants and from 21.122 to 25.1 kg/m^2 26 in infected participants. BMI was significantly different between case and control groups in three studies24, 25, 27.

Table 3: Prevalence Data: HIV infected (treated and untreated) vs non infected

Author, Year	Setting	Population	Case HIV+	Control HIV-	ART	Diagnosis	Prevalence case %	Prevalence control %	p-value
Amusa, 2015	Nigeria	200 adults	n=150, 62.6% female mean age=40.6	n=50, 60% female mean age=40.2	Not stated	FPG, criteria not stated	28	4	0.01
Anastos, 2010	Rwanda	824 women	n=606 mean age=42.4 mean BMI=21.1	n=218 mean age=34.7 Mean BMI=20.6	Not stated	Self report or WHO criteria	0.5	0.5	0.98
Becker, 2010	South Africa	60 adults	n=30, 33% female mean age=43 mean BMI=25	n=30, 40% female mean age=54 mean BMI=28	Not on treatment	Prescription of anti-diabetic medication or diagnosis upon admission	3	23	0.05
Brand, 2014	South Africa	20 black males requiring amputation	n=10 mean age=47 mean BMI=22.4	n=10 mean age=62 mean BMI=25.3	Not on treatment	WHO criteria or prescription of anti-diabetic medication	50	0	<0.05
Edwards, 2015	Kenya	2206 adults	n=210, 69% female mean	n=1996, 71% female	First line ART utilized tenofovir/lamivudin	WHO criteria	4.8	15.0	<0.001

			age=43	mean age=49	e/efavirenz; second line lopinavir/ritonavir instead of efavirenz				
Fourie, 2010	South Africa	600 adults	n=300, 61% female mean age=44 mean BMI=22.9	n=300, 61% female mean age=44 mean BMI=22.8	Not on treatment	IDF criteria	36.6	43.7	0.64
Ngatchou, 2013	Cameroon	204 adults	n=108, 74% female mean age=39 mean BMI=25.1	n=96, 72% female mean age =41 mean BMI=28.1	Not on treatment	WHO criteria	26	1	0.01
Maganga, 2015	Tanzania	454 adults	n=301, 67.8% female mean age=37 (untreated) and 40 (treated) mean BMI=22.0 (untreated) and 23.7(treated)	n=153, 61,4% female mean age=38 mean BMI=23.8	n=151 not on treatment n=150 on treatment - 21% on protease inhibitors (lopinavir and ritonavir); rest on other ART: nevirapine, efavirenz, tenofovir, stavudine, zidovudine	WHO criteria	9.3	5.2	0.04 (untreated vs control) and 0.001 (treated vs control)

ART – anti retro-viral therapy, HIV – Human immunodeficiency virus, FPG – fasting plasma glucose, BMI – Body mass index, WHO – world health organization, IDF – International diabetes federation

Prevalence of diabetes in HIV infected treated compared to untreated participants

A meta-analysis of five studies comparing HIV treated (n=1120) to untreated participants (n=828) (Table 4) using a random effects model (I=53.25%) indicated no significant association between HIV treatment and diabetes prevalence (RR=1.380, 95% CI=0.663- 2.872, p=0.389), Figure 4. The majority of included participants were female (range 5834-75%31), and mean age ranged from 32.732 to 44.2 years31 (age was not stated for Manuthu et al34). All treated participants were receiving cART (therapy not stated by Kagaruki et al33). Where stated, age was higher in treated compared to untreated participants31-33, yet significance was not stated. Mean BMI was only reported in two studies, and was in the WHO healthy weight category (22kg/m^2) for both groups in one study32, and in the WHO overweight category (26.5kg/m^2) for both groups in the second study31.

Table 4: Prevalence Data: HIV infected treated vs untreated

Author, Year	Setting	Population	Case Treated	Control Untreated	ART	Diagnosis	Prevalence Case %	Prevalence Control %	p-value
Kagaruki, 2014	Tanzania	671 participants, 70.5% female mean age=38.7	n=354, 67.8% female mean age=40.6	n=317, 73.5% female mean age=36.7	Not stated	WHO criteria	3.7	4.7	Not stated
Tesfaye, 2014	Ethiopa	374 participants, 68% female Mean age=32.7	n=188, 63.8% female mean age=32.7 mean BMI=22.1	n=186, 68.8% female mean age=32.6 Mean BMI=22.2	58% on regimen containing efavirenz and 42% on nevirapine as NNRTI	IDF criteria	33.5	21.5	<0.05
Manuthu, 2008	Kenya	295 participants, 58% female	n=134	n=161	82.7% on d4t-based regimen, 51.1% on d4T+3TC+nevirapine 31.6% on d4T+3TC+efavirenz. 17.3% on AZT-based regimens 13.5% on AZT+3TC+efavirenz 3.8% on AZT+3TC+nevirapine; one PI-based regimen was AZT+3TC+lopinavir.	OGTT, criteria not stated	1.5	1.2	0.85
Mohammed, 2015	Ethiopia	393 adults, 66.9% female mean age=37.9	n=284	n=109	32.1% used the drug combination zidovudine + lamivudine + nevirapine	WHO criteria	8.5	0.9	0.006

Nsagha, 2015	Cameroon	215 participants, 74.9% female Mean age 44.2 years Mean BMI=26.47	n=160, 77.5% female mean age=44.7 mean BMI=26.94	n=55, 67.3% female mean age=38.6 Mean BMI=25.09	AZT+3TC+efavirenx =1.3%, AZT+3TC+nevirapine =50%, TDF+3TC+efavirenz =27.5%, TDF+3TC+nevirapine= 13.1%, TDF+3TC+ lopinavir= 8.1%	WHO criteria	1.9	3.6	0.463

ART – anti retro-viral therapy, WHO – world health organization, BMI – Body mass index, IDF – International diabetes federation, NNRTI – non nucleotide reverse transcriptase, d4t – stavudine, 3TC – lamivudine, , AZT - zidovudine, PI – protease inhibitor, OGTT – oral glucose tolerance test, TDF – tenofovir

DISCUSSION

This systematic review and meta-analysis of African studies showed no statistically significant association between HIV infection or cART exposure, and diabetes prevalence. This is contrary to study findings of international studies in Europe and North America that have shown a higher prevalence of diabetes in HIV infected compared to uninfected participants35, particularly when treated with cART 1, 3, 5.

Incidence rates of diabetes in patients with HIV were described in person years of follow up and ranged considerably among the included studies. Cumulative incidence rate for the included studies was 0.017 person years. For comparison, the incidence rate of diabetes in a healthy American population in 2012 was lower at 0.00836. Individually, four included papers reported lower incidence rates than the American population, and four reported higher incidence rates. There were no obvious differences between these studies in terms of age, sex, and duration of follow up, BMI or treatment; yet studies with larger sample sizes seemed to show higher prevalence rates. A systematic review of diabetes in Sub-Saharan Africa4 found only one study reporting an incidence rate of 0.029 in healthy adults in Kinshasa37. In the present systematic review, only one included study on HIV infected participants reported higher incidence rates than the healthy adults in Kinshasa16. Therefore from the limited data available, and from the included studies in this systematic review it does not seem that incidence is higher in populations infected with HIV in Africa than in a healthy ageing African population.

Diabetes incidence and prevalence rates have been reported internationally in HIV infected and treated patients. De Wit et al (2008) reported diabetes incidence rates of 0.006 (and an incidence rate of 0.004 for definite cases of diabetes) from the D:A:D study38. They examined 33 389 HIV infected patients from 212 clinics in Europe, USA, Argentina, and Australia, and found that treatment with stavudine increased the RR of diabetes by 1.19 per year of exposure (conversely, treatment with ritonavir and nevirapine decreased risk of diabetes). Interestingly, controlling for lipodystrophy did not modify this relationship, and a direct effect of treatment on mitochondrial toxicity was thus suggested. Baseline prevalence of diabetes in this study was 2.9%. Findings from the Multicentre AIDS cohort study (MACS) showed a diabetes incidence of 0.047 in HIV infected white males who were on cART vs 0.017 in those who were cART naïve, however this study used only a single increased fasting plasma glucose as their diagnostic criteria39. Nigatu et al, in 2013 conducted a systematic review looking at incidence of various comorbidities, including diabetes, with HIV infection, and found a combined diabetes incidence rate of 0.006 (with a range of 0.0042-0.036) in a sample of 44 484 individuals40. In the studies included in their systematic review, ART exposure increased incidence rates when compared to ART naïve patients. Conversely, Tripathi et al (2014) found that 6816 HIV infected patients (of which over 80% were treated with ART) had lower diabetes incidence rates than matched, non infected individuals (0.01135 vs 0.0136)41. Similarly, Nix et al in 2014 stated that their summary of the literature found a similar decreased incidence of diabetes in HIV infected individuals compared to

controls42. The present systematic review found a combined diabetes incidence rate of 0.0165 in HIV infected cART treated African patients, which is higher than incidence rates found in all of the above-mentioned studies except for the males in the MACS study. Therefore, although incidence does not seem to be higher in HIV infected patients in Africa compared to a normal ageing population in Africa; diabetes incidence in HIV infected people in Africa does appear to be higher than rates reported internationally for HIV infected patients, and those reported for a healthy American population.

It is possible that this higher incidence of diabetes in African HIV infected individuals compared to international incidence data is in part explained by a greater susceptibility to diabetes in African populations, regardless of HIV status. As many African populations are undergoing rapid transitions, the toxic combination of early life undernutrition in utero and infancy, combined with excessive weight gain in later life may be contributing to diabetes susceptibility 43. In fact, in studies included in this systematic review where mean BMI was reported, a substantial proportion of participants infected with HIV were overweight or obese. This presents a different picture to the undernourished HIV infected individual previously associated with Africa, and may explain a higher incidence of diabetes as an effect of lifestyle rather than a HIV disease related risk. Although this systematic review has not shown a higher prevalence of diabetes in HIV infected individuals compared to uninfected individuals, it does support the importance of screening for diabetes in African populations infected with HIV where diabetes incidence appears to be high. Furthermore, these findings reinforce the importance of managing and screening for metabolic disease, such as diabetes as part of routine clinical care of patients infected with HIV in order to support continuity of care44.

It is important to note that since none of the included studies were randomised, and there were too few studies for subgroup analyses, we cannot account for differences in disease course or lifestyle factors that confound exposure to cART or diabetes risk. Similarly, differences in cART exposure may be associated with regression or cure of illnesses in HIV, or with increased risk factors for diabetes. The mean age of included participants was generally lower than 45 years, which may have influenced the cumulative incidence reported in this review, since age influences diabetic progression. There was also heterogeneity in the method of diagnosis of diabetes between studies, which could have confounded results. Although all of the diagnosis methods included in this systematic review were well recognized (see Table 4), future diabetes screening programmes should strive to utilise gold standard diagnosis methods such as OGTT or HbA1c values11. The findings of this systematic review are further limited by the high risk of bias of included studies, largely due to confounding factors and limited blinding. Furthermore, the small sample size of included studies, as well as small number of studies available limit the conclusions that can be drawn. These limitations highlight the need for larger studies to be conducted examining diabetes incidence and prevalence in people with HIV in Africa, with focus on careful blinding and consideration of confounders.

In conclusion, this meta-analysis shows no significant association between HIV infection or treatment and diabetes prevalence in African population studies. Furthermore, incidence of diabetes in Africa in HIV infected patients on cART is no greater than in a normal ageing population, yet is higher than incidence rates in HIV infected individuals outside of Africa. Larger case control studies with effective blinding and consideration of confounders need to be conducted in Africa in order to further elucidate these associations in comparison to international findings. Currently, HIV infection and cART do not seem to predispose patients in Africa to diabetes, however high incidence rates warrant focus on screening and preventative programmes for HIV infected people living in Africa.

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CONTRIBUTION STATEMENT

AP contributed to conception and design; acquired, analysed and interpreted the data; drafted the article, and approved the final version for publication. RJM acquired the data, revised the article and approved the final version for publication. LS acquired the data, revised the article and approved the final version for publication. JAG acquired the data, revised the article and approved the final version for publication. LKM acquired the data, revised the article and approved the final version for publication. DMA acquired the data, revised the article and approved the final version for publication. SAN contributed to conception and design, acquired and interpreted the data, revised the article and approved the final version for publication. We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

DATA SHARING

No additional data available

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FIGURE LEGENDS

Figure 1. Flow diagram of article selection process, and reasons for inclusion and exclusion

Figure 2. Incidence rates of diabetes in HIV infected and treated participants in Africa

Figure 3. Meta-analysis of studies comparing diabetes in HIV-infected and HIV-uninfected participants.

Figure 4. Meta-analysis of studies comparing diabetes in HIV-infected treated and untreated participants.

Figure 5. Risk of bias assessment for studies included in the analysis

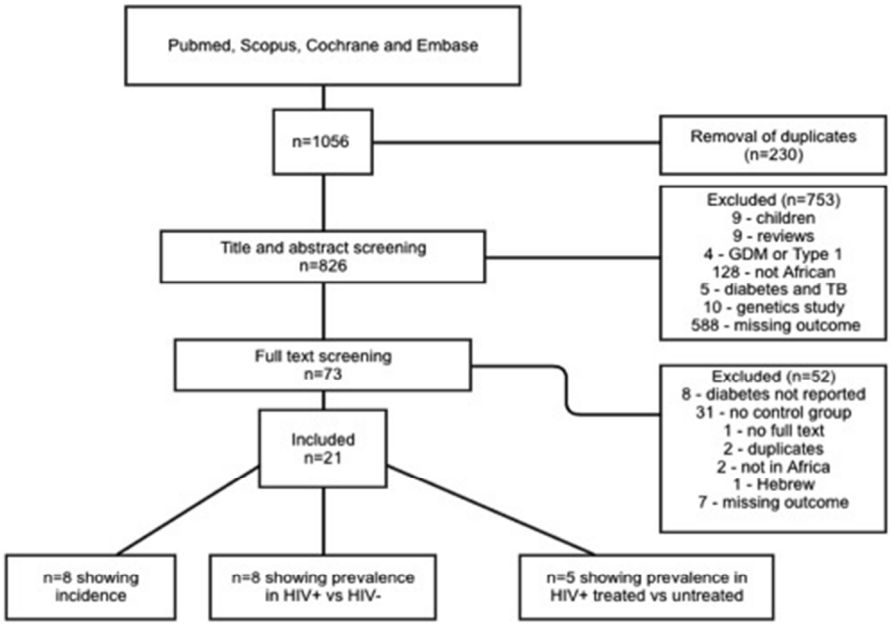

Figure 1. Flow diagram of article selection process, and reasons for inclusion and exclusion

196x134mm (72 x 72 DPI)

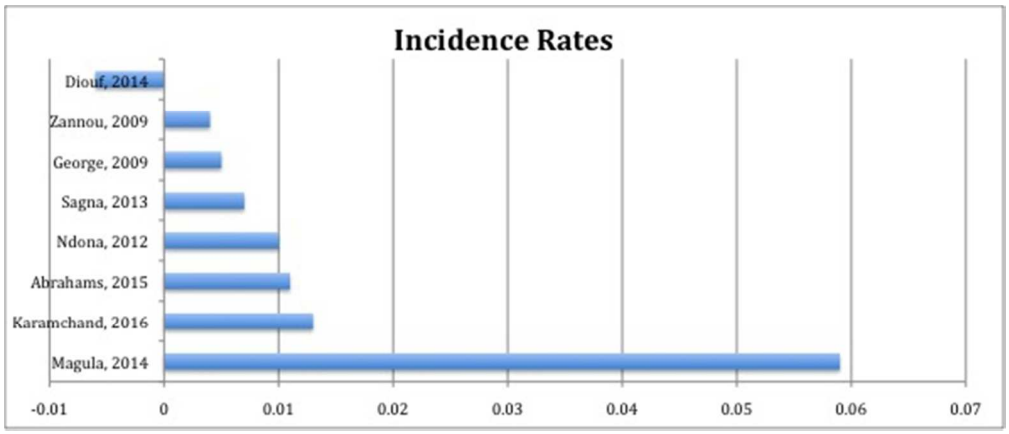

Figure 2. Incidence rates of diabetes in HIV infected and treated participants in Africa

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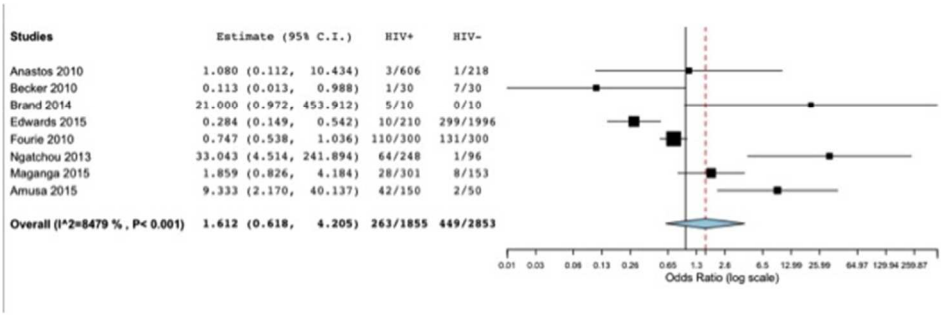

Figure 3. Meta-analysis of studies comparing diabetes in HIV-infected and HIV-uninfected participants.

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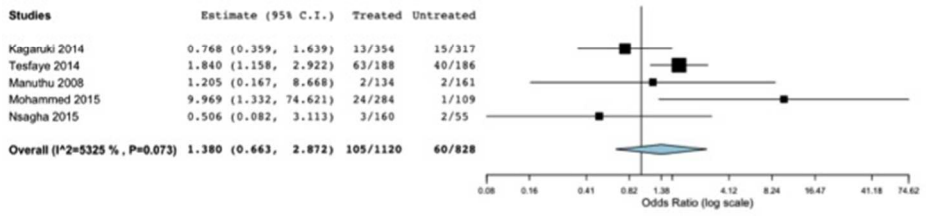

Figure 4. Meta-analysis of studies comparing diabetes in HIV-infected treated and untreated participants.

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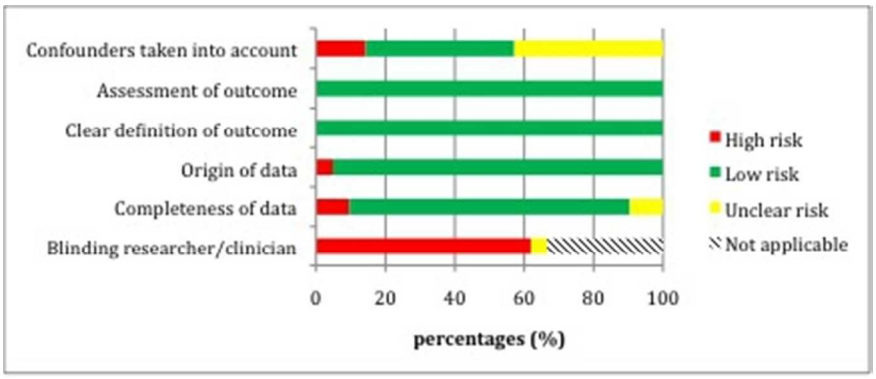

Figure 5. Risk of bias assessment for studies included in the analysis

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3,4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4,5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4,5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 5-6,Table 1-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 5, Figure 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 5-6,Table 1-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 5,6, Figure 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 5, Figure 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8-9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Incidence and prevalence of Type 2 diabetes mellitus with HIV infection in Africa: A systematic review and meta analysis

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Incidence and prevalence of Type 2 diabetes mellitus with HIV infection in Africa: A systematic review and meta analysis

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ABSTRACT

Objectives: This systematic review aims to investigate the incidence and prevalence of diabetes in HIV infected patients in African populations. **Setting:** Only studies reporting data from Africa were included. **Participants:** A systematic search was conducted using four databases for articles referring to HIV infection and antiretroviral therapy, and type 2 diabetes mellitus in Africa. Articles were excluded if they reported data on children, animals or type 1 diabetes exclusively. **Main outcome measures:** Incidence of diabetes and prevalence of diabetes. Risk ratios were generated for pooled data using random effects models. Bias was assessed using an adapted Cochrane Collaboration bias assessment tool. **Results:** Of 1056 references that were screened, only 20 were selected for inclusion. Seven reported the incidence of diabetes in HIV infected patients, eight reported the prevalence of diabetes in HIV infected vs uninfected individuals, and five reported prevalence of diabetes in HIV treated vs untreated patients. Incidence rates ranged from 4 to 59 per 1000 person years. Meta-analysis showed no significant differences between diabetes prevalence in HIV infected vs uninfected individuals (RR=1.61, 95% CI=0.62-4.21, p=0.33), or between HIV treated vs untreated patients (RR=1.38, 95% CI=0.66-2.87, p=0.39), and heterogeneity was high in both meta-analyses (I2=87% and 52% respectively). **Conclusion:** Meta-analysis showed no association between diabetes prevalence and HIV infection or ART, however these results are limited by the high heterogeneity of the included studies and moderate to high risk of bias, as well as, the small number of studies included. There is a need for well designed prospective longitudinal studies with larger population sizes to better assess incidence and prevalence of type 2 diabetes in African patients with HIV. Furthermore, screening for diabetes using gold standard methods in this population is necessary. **Trial Registration:** PROSPERO: 42016038689.

KEYWORDS

Type 2 diabetes, HIV, Africa, combination antiretroviral therapy, incidence, prevalence

STRENGTHS AND LIMITATIONS OF THE STUDY

- This is the first systematic review of the literature examining associations between HIV infection and treatment with diabetes incidence and prevalence in Africa.
- The stringent inclusion criteria used is a strength of this systematic review.
- Differences in methods of diabetes diagnosis across studies is a limitation.
- Heterogeneity and moderate to high risk of bias across studies is a limitation.
- The small number of studies meeting the inclusion criteria is a limitation.

BACKGROUND

The introduction of combination antiretroviral therapies (cARTs) in the treatment of human immunodeficiency virus (HIV) infection has resulted in significant extension of the predicted lifespan of HIV infected patients[1]. Consequently, patients with HIV are potentially at greater risk of developing non-communicable diseases (NCDs) than due to the ageing process alone; as the disease itself[2], and treatments used to combat HIV, are associated with metabolic complications[3].

Type 2 diabetes mellitus is one such disease that is becoming increasingly common, specifically in Africa due to rapidly transitioning lifestyles. An estimated 12.1 million people were living with diabetes in Africa in 2010[4] and it is predicted that this will increase to 23.9 milllion by 2030. Besides associations with age, obesity, sex, and race[5]; recent studies have associated diabetes with HIV infection, and with cART[1, 3, 5]. The mechanisms underlying these associations are not fully elucidated, but may reflect chronic systemic inflammation in response to HIV infection despite treatment[6, 7], antiretroviral drug-induced mitochondrial dysfunction, lipodystrophy and comorbidities[5]. Conversely, some studies have shown a decreased incidence of diabetes in HIV infected compared to uninfected individuals[8, 9]. Diabetes is associated with increased morbidity and mortality, an estimated 1.5 million deaths were attributed directly to diabetes in 2012[10], and the implications of HIV infection and treatment on the incidence of diabetes is therefore important to explore. The aim of this systematic review is to investigate the incidence of diabetes in HIV infected patients in Africa, as well as, the prevalence of diabetes in HIV infected and cART treated patients in comparison to non infected and non treated individuals.

METHODS

The systematic review focused on the associations between HIV infection, ARV therapy and diabetes mellitus. This review was registered in the PROSPERO registry for systematic reviews (Registration number 42016038689)[11], and was conducted in accordance with the PRISMA guidelines[12].

Search Strategy

The search for this systematic review was conducted in May 2016 and included terms in the determinants of HIV infection and antiretroviral therapy, the domain of Africa, and the outcome of diabetes. Restrictions included age (adolescent or older), date of publication (after January 01 2008 due to the presence of an existing review examining prevalence if diabetes in HIV conducted in 2008[13]). The title and abstracts of articles in Pubmed, Scopus, the Cochrane library, and Embase were searched; and a sample of the Embase search strategy is available online as a supplementary file. Keywords used included: 'HIV', 'diabetes', 'Africa', and 'antiretroviral therapy'.

Study Selection

All observational studies (cohort, case-control, and cross-sectional) that assessed the relationship between HIV seropositivity with or without cART therapy, and diabetes in Africa were included. Animal studies, biomolecular studies, studies not written in English or French, case reports, and secondary analyses, were excluded. Studies reporting outcomes in children or pregnant women, or reporting type 1 diabetes outcomes only, or not reporting diabetes incidence or prevalence (but hyperglycemia or impaired glucose tolerance for example) were also excluded. Studies that did not report prevalence of diabetes in HIV infected compared to HIV uninfected participants; or prevalence of diabetes between cART exposure compared to untreated HIV infected patients; or incidence of diabetes in HIV infected patients were excluded. Authors of individual studies defined the criteria for diabetes diagnoses, and variant criteria were included provided diagnosis was made using a recognised score for a fasted blood glucose, or an oral glucose tolerance test (OGTT), or HbA1c values[14].

Screening and data extraction

Two independent reviewers (AP, RJM) independently screened all articles retrieved by the search strategy by title and abstract for eligibility according to inclusion and exclusion criteria. Any discrepancies between the two reviewers were discussed and consensus was reached. The full text was accessed if necessary for further clarification. Full texts of eligible articles were then retrieved and divided amongst all reviewers. If no full text was available, one attempt was made to contact the author. Each full text was assessed for eligibility by one reviewer, and a second reviewer was available for consultation. Data extraction was then performed using a standardised data extraction form. One reviewer (AP) reassessed data extraction for all eligible full texts. Data of interest was study design, study setting and country, population, age, body mass index (BMI), number of patients included in each group, control population, cART treatment at the time of inclusion, duration of cART treatment, method of diabetes diagnosis, incidence of known risk factors for diabetes such as obesity, treatment provided for diabetes, incidence of diabetes in the control group and group with HIV and/or antiretroviral therapy, when applicable OR/RR, and follow-up duration. In cases of incomplete data, one attempt was made to contact the corresponding author by email and if no response was received the paper was excluded.

Data synthesis

Three separate analyses were performed for articles that examined incidence of diabetes; prevalence of diabetes in HIV infected vs uninfected participants; and prevalence of diabetes in HIV infected and treated vs untreated participants. Meta-analysis was conducted for articles with sufficiently homogenous outcome measures and study designs. The principle summary measure used was risk ratio (RR), and in cases of substantial heterogeneity (I2>50%) according to the Cochrane handbook[15], a binary random effects model (using the DerSimonian-Laird method) was applied. Analyses were conducted using OpenMetaAnalyst. A

priori subgroup analyses based on geographical localisation, age, ART medication/treatment strategy and duration, severity of HIV, and method of diabetes diagnosis were not possible due to insignificant sub categorisation of data and insufficient number of included studies[15].

Risk of bias assessment

Studies were assessed for risk of bias using the Evidence Partner's risk of bias tool for cohort studies[16] as 'low risk', 'medium-low risk', 'medium-high risk', 'high risk', or 'not applicable' for the categories of: similarity of intervention, adequacy of follow up, assessment of outcome, assessment of prognostic factors, matching relevant variables between case and control, presence of outcome of interest at start of the study, assessment of exposure, and selection of populations. This tool is available as a supplementary file.

RESULTS

The search provided 1056 results. After screening, 20 articles met the eligibility criteria[17-36] and were included in the analysis (Figure 1). Of these, 7[17-23] articles reported incidence of diabetes in HIV infected participants, 8[24-31] reported prevalence of diabetes in HIV infected participants compared to uninfected controls, and 5[32-36] reported prevalence of diabetes in HIV infected participants on treatment compared to untreated controls. In included studies, diabetes was diagnosed if participants were being treated for diabetes, or by oral glucose tolerance test (OGTT). As summarised in Table 1, four main criteria were used: World Health Organisation (WHO), American Diabetes Association (ADA), International Diabetes Federation (IDF), and National Cholesterol Education Programme (NCEP) criteria.

Table 1. Overview of diagnostic criteria used in the included studies

Criteria used	Definitions
WHO	Fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl).
ADA	Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) or 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during OGTT (75g) or A1C ≥6.5% (48 mmol/mol) or Random plasma glucose ≥200 mg/dL (11.1 mmol/L)
NCEP cut offs	Fasting plasma glucose ≥5.6 mmol/L
IDF	FPG ≥ 100 mg/dl (5.6 mmol/L)

WHO – world health organisation, ADA – American diabetes association, OGTT – oral glucose tolerance test, A1C - NCEP - National Cholesterol Education Programme, IDF – International diabetes federation

Risk of bias

A summary of the risk of bias assessment is presented in Figure 2. All included studies were observational, and 15 (71%) were case control studies. In 5% of studies there was a high risk of bias due to HIV treatment not being stated. In 25% of studies there was a medium-high risk of bias due to confounding variables. Four (20%) of studies had medium-low risk of bias due to diabetes

diagnosis criteria. Three (14%) included studies were published conference proceedings.

Incidence of diabetes in HIV infected participants

Seven studies reported diabetes incidence in HIV infected participants (n=57006; Table 2). One of the included studies compared incidence in treated vs untreated participants[21], and another compared incidence in infected vs uninfected participants[20]. The rest of the studies assessed incidence in HIV infected and treated participants with no control group. Most participants were on cART, except for participants in the Sagna et al study who were on first line therapy, which was not clearly specified[22]. Mean age of participants ranged from 33.5 years[17] to 38 years [19, 23](age was not stated by Magula et al[20]). Mean BMI ranged from 19.2kg/m^2[23] to 27.9kg/m^2[17], and was not stated in one of the studies[20]. Mean duration of follow up ranged from 1.56 years[19] to 5.5 years[17], and the total number of participants followed up to completion was n=56875. The majority of participants were female in all studies where sex was stated. Incidence of diabetes was reported as absolute incidence, cumulative incidence, incidence proportion, and incidence rate per 1000 person years. Incidence rates ranged from 4[23] to 59[20], Figure 3. The combined incidence rate for all the included studies over 89640 person years of follow up was 17.4.

Author, Year	Setting	Population	Case	Control	ART	Follow up Mean/median	Diagnosis of diabetes	Prevalence at Baseline n(%)	Prevalence at follow-up n(%)	Cumulative Incidence	Incidence Proportion	Incidence Rate (per 1000 person years)	p-value

Abrahams, 2015	South Africa	103 women Mean age =33.5 Mean BMI=27.9	NA	NA	Stavudine/lamivudine	5.5 years n=94	ADA criteria	1 (1.0)	7 (7.5)	6.5%	5.83%	11	0.07
George, 2009	South Africa	42 black participants, 65% female mean age=34.4 mean BMI=22.7	NA	NA	Stavudine/Zidovudine	2 years n=42	NCEP cut off	1(2.4)	1(2.5)	0.1%	0.001 %	5	>0.05
Karamchand, 2016	South Africa	56298 participants, 64% female Mean age=38.14 Mean BMI=25.95	NA	NA	First line NNRTI regimen containing efavirenz or nevirapine	1.56 years n=56298	Prescription of anti-diabetic medication	0(0)	1500 (2.66)	2.66%	2.66%	13	Not reported
Magula, 2014	South Africa	238 participants	n=150 treated	n=88 uninfected	Initiated - tenofovir, lamivu- dine, efavirenz/nevirapine	2 years n=150	WHO criteria	0(0)	13(8.66)	8.66%	8.66%	59	Not reported
Ndona, 2012	DRC	102 participants, 51% female, mean age= 43.4 mean BMI=23.1	n=49 HIV+ treated	n=53 HIV+ untreated	stavudine + lamivudine, zidovudine + lamivudine + nevirapine, or efavirenz	4 years n=102	WHO criteria	Not stated	5(4.9)	4.9%	4.9%	10	0.06
Sagna, 2013	Burkino Faso	144 participants, Mean age=37	NA	NA	Not stated (first line therapy)	3 years n=128	Not stated	Not stated	3(2.3)	2.3%	2.1%	7	Not reported
Zannou,	Benin	79	NA	NA	All started	2 years	WHO	0(0)	6(7.6)	7.6%	7.6%	4	Not

2009		participants, 59.5% female mean age= 38 mean BMI=19.2			combination therapy. Lamivudine + stavudine +efavirenz	n=61	criteria						reported

Table 2: Incidence Data

ART – anti retro-viral therapy, BMI – Body mass index, OGTT – oral glucose tolerance test, ADA – American Diabetes Association, NNRTI – non nucleotide reverse transcriptase inhibitors, WHO – world health organization, NCEP – National Cholesterol Education Programme, DRC – Democratic Republic of Congo, HIV – Human immunodeficiency virus

Prevalence of diabetes in HIV infected compared to uninfected participants

Table 3 shows the data for eight studies included in a meta-analysis comparing HIV infected (n=1715) to uninfected participants (n=2853). The majority of included participants were female, except for the study conducted by Brand et al[27], who only included males, and by Becker et al[26], where the majority of participants were male. In four of the included studies, infected participants were not on treatment[26, 27, 29, 31] and in a further two[24, 25], treatment was not stated. The remaining two studies examined participants on cART. Mean age ranged from 34.7 years[25] to 62 years[27] in uninfected participants and 37 years[30] to 47 years[27] in infected participants. Age was significantly different between the case and control groups in three studies[26-28]. Mean BMI ranged from 20.6kg/m^2 [25] to 28.1kg/m^2[31] in uninfected participants and from 21.1kg/m^2[25] to 25.1kg/m^2[31] in infected participants. BMI was significantly different between case and control groups in three studies[26, 27, 31]. A meta-analysis using a random effects model (I2=84.79%) indicated no significant association between HIV infection and diabetes prevalence (RR=1.61, 95% CI=0.62- 4.21, p=0.33), Figure 4.

Table 3: Prevalence Data: HIV infected (treated and untreated) vs non infected

Author, Year	Setting	Population	Case HIV+	Control HIV-	ART	Diagnosis	Prevalence case %	Prevalence control %	p-value
Amusa, 2015	Nigeria	200 adults	n=150, 62.6% female mean age=40.6	n=50, 60% female mean age=40.2	Not stated	FPG, criteria not stated	28.0	4.0	0.01
Anastos, 2010	Rwanda	824 women	n=606 mean age=42.4 mean BMI=21.1	n=218 mean age=34.7 Mean BMI=20.6	Not stated	Self report or WHO criteria	0.5	0.5	0.98
Becker, 2010	South Africa	60 adults	n=30, 33% female mean age=43 mean BMI=25	n=30, 40% female mean age=54 mean BMI=28	Not on treatment	Prescription of anti-diabetic medication or diagnosis upon admission	3.0	23.0	0.05
Brand, 2014	South Africa	20 black males requiring amputation	n=10 mean age=47 mean BMI=22.4	n=10 mean age=62 mean BMI=25.3	Not on treatment	WHO criteria or prescription of anti-diabetic medication	50.0	0.0	<0.05
Edwards, 2015	Kenya	2206 adults	n=210, 69% female mean	n=1996, 71% female	First line ART utilized tenofovir/lamivudin	WHO criteria	4.8	15.0	<0.01

			age=43	mean age=49	e/efavirenz; second line lopinavir/ritonavir instead of efavirenz				
Fourie, 2010	South Africa	600 adults	n=300, 61% female mean age=44 mean BMI=22.9	n=300, 61% female mean age=44 mean BMI=22.8	Not on treatment	IDF criteria	36.6	43.7	0.64
Maganga, 2015	Tanzania	454 adults	n=301, 67.8% female mean age=37 (untreated) and 40 (treated) mean BMI=22.0 (untreated) and 23.7(treated)	n=153, 61,4% female mean age=38 mean BMI=23.8	n=151 not on treatment n=150 on treatment - 21% on protease inhibitors (lopinavir and ritonavir); rest on other ART: nevirapine, efavirenz, tenofovir, stavudine, zidovudine	WHO criteria	9.3	5.2	0.04 (untreated vs control) and 0.001 (treated vs control)
Ngatchou, 2013	Cameroon	204 adults	n=108, 74% female mean age=39 mean BMI=25.1	n=96, 72% female mean age =41 mean BMI=28.1	Not on treatment	WHO criteria	26.0	1.0	0.01

ART – anti retro-viral therapy, HIV – Human immunodeficiency virus, FPG – fasting plasma glucose, BMI – Body mass index, WHO – world health organization, IDF – International diabetes federation

Prevalence of diabetes in HIV infected treated compared to untreated participants

Table 4 shows the data for five studies included in the meta-analysis comparing HIV treated (n=1120) to untreated participants (n=828). The majority of included participants were female (range 58%[34] to 75% female[36]), and mean age ranged from 32.7 years[33] to 44.2 years[36] (age was not stated for Manuthu et al[34]). All treated participants were receiving cART (therapy not stated by Kagaruki et al[32]). Where stated, age was higher in treated compared to untreated participants[32, 33, 36], yet significance was not stated for these age differences. Mean BMI was only reported in two studies, and was in the WHO healthy weight category (22kg/m^2) for both groups in one study[33], and in the WHO overweight category (26.5kg/m^2) for both groups in the second study[36]. A meta-analysis using a random effects model (I2=53.25%) indicated no significant association between HIV treatment and diabetes prevalence (RR=1.38, 95% CI=0.66- 2.87, p=0.39), Figure 5.

Table 4: Prevalence Data: HIV infected treated vs untreated

Author, Year	Setting	Population	Case Treated	Control Untreated	ART	Diagnosis	Prevalence Case %	Prevalence Control %	p-value
Kagaruki, 2014	Tanzania	671 participants, 70.5% female mean age=38.7	n=354, 67.8% female mean age=40.6	n=317, 73.5% female mean age=36.7	Not stated	WHO criteria	3.7	4.7	Not stated
Manuthu, 2008	Kenya	295 participants, 58% female	n=134	n=161	82.7% on d4t-based regimen, 51.1% on d4T+3TC+nevirapine 31.6% on d4T+3TC+efavirenz. 17.3% on AZT-based regimens 13.5% on AZT+3TC+efavirenz 3.8% on AZT+3TC+nevirapine; one PI-based regimen was AZT+3TC+lopinavir.	OGTT, criteria not stated	1.5	1.2	0.85
Mohammed, 2015	Ethiopia	393 adults, 66.9% female mean age=37.9	n=284	n=109	32.1% used the drug combination zidovudine + lamivudine + nevirapine	WHO criteria	8.5	0.9	<0.01
Nsagha, 2015	Cameroon	215 participants, 74.9% female Mean age 44.2 years Mean BMI=26.47	n=160, 77.5% female mean age=44.7 mean BMI=26.94	n=55, 67.3% female mean age=38.6 Mean BMI=25.09	AZT+3TC+efavirenx =1.3%, AZT+3TC+nevirapine =50%, TDF+3TC+efavirenz =27.5%, TDF+3TC+nevirapine= 13.1%, TDF+3TC+ lopinavir= 8.1%	WHO criteria	1.9	3.6	0.46

Tesfaye, 2014	Ethiopa	374 participants, 68% female Mean age=32.7	n=188, 63.8% female mean age=32.7 mean BMI=22.1	n=186, 68.8% female mean age=32.6 Mean BMI=22.2	58% on regimen containing efavirenz and 42% on nevirapine as NNRTI	IDF criteria	33.5	21.5	<0.05

ART – anti retro-viral therapy, WHO – world health organization, BMI – Body mass index, IDF – International diabetes federation, NNRTI – non nucleotide reverse transcriptase, d4t – stavudine, 3TC – lamivudine, , AZT - zidovudine, PI – protease inhibitor, OGTT – oral glucose tolerance test, TDF – tenofovir

DISCUSSION

This systematic review and meta-analysis of African studies showed no statistically significant association between HIV infection or cART exposure, and diabetes prevalence. This is contrary to study findings of international studies in Europe and North America that have shown a higher prevalence of diabetes in HIV infected compared to uninfected participants[37], particularly when treated with cART [1, 3, 5].

Incidence rates of diabetes in patients with HIV were described per 1000 person years of follow up and ranged considerably among the included studies. Cumulative incidence rate for the included studies was 17.4. For comparison, the incidence rate of diabetes in a healthy American population in 2012 was lower at 7.8[38]. Individually, three included papers reported lower incidence rates than the American population, and four reported higher incidence rates. There were no obvious differences between these studies in terms of age, sex, and duration of follow up, BMI or treatment; yet studies with larger sample sizes seemed to show higher incidence rates. A systematic review of diabetes in Sub-Saharan Africa[4] found only one study reporting an incidence rate of 29 in healthy adults (> 40 years) in Kinshasa[39]. In the present systematic review, only one included study on HIV infected participants reported higher incidence rates than the healthy adults in Kinshasa[20]. Therefore from the limited data available, and from the included studies in this systematic review it does not seem that incidence is higher in populations infected with HIV in Africa than in a healthy ageing African population.

Diabetes incidence and prevalence rates have been reported internationally in HIV infected and treated patients. De Wit et al (2008) reported diabetes incidence rates of 6 (and an incidence rate of 4 for definite cases of diabetes) from the D:A:D study[40]. They examined 33 389 HIV infected patients from 212 clinics in Europe, USA, Argentina, and Australia, and found that treatment with stavudine increased the RR of diabetes by 1.19 per year of exposure (conversely, treatment with ritonavir and nevirapine decreased risk of diabetes). Interestingly, controlling for lipodystrophy did not modify this relationship, and a direct effect of treatment on mitochondrial toxicity was thus suggested. Baseline prevalence of diabetes in this study was 2.9%. Findings from the Multicentre AIDS cohort study (MACS) showed a diabetes incidence of 47 in HIV infected white males who were on cART vs 17 in those who were cART naïve, however this study used only a single increased fasting plasma glucose as their diagnostic criteria[41]. Nigatu et al, in 2013 conducted a systematic review looking at incidence of various comorbidities, including diabetes, with HIV infection, and found a combined diabetes incidence rate of 6 (with a range of 4.2-36) in a sample of 44 484 individuals[42]. In the studies included in their systematic review, ART exposure increased incidence rates when compared to ART naïve patients. Conversely, Tripathi et al (2014) found that 6816 HIV infected patients (of which over 80% were treated with ART) had lower diabetes incidence rates than matched, non-infected individuals (11.4 vs 13.6)[8]. Similarly, Nix et al in 2014 stated that their summary of the literature found a similar decreased incidence of diabetes in HIV infected individuals compared to

controls[9]. The present systematic review found a combined diabetes incidence rate of 17.4 in HIV infected cART treated African patients, which is higher than incidence rates found in all of the above-mentioned studies except for the males in the MACS study. Therefore, although incidence does not seem to be higher in HIV infected patients in Africa compared to a normal ageing population in Africa; diabetes incidence in HIV infected people in Africa does appear to be higher than rates reported internationally for HIV infected patients, and those reported for a healthy American population.

It is possible that this higher incidence of diabetes in African HIV infected individuals compared to international incidence data could be explained by a greater susceptibility to diabetes in African populations, regardless of HIV status. As many African populations are undergoing rapid transitions, the toxic combination of early life undernutrition in utero and infancy, combined with excessive weight gain in later life may be contributing to diabetes susceptibility [43]. In fact, in studies included in this systematic review where mean BMI was reported, a substantial proportion of participants infected with HIV were overweight or obese. This presents a different picture to the undernourished HIV infected individual previously associated with Africa, and may explain a higher incidence of diabetes as an effect of lifestyle rather than a HIV disease related risk. Although this systematic review has not shown a higher prevalence of diabetes in HIV infected individuals compared to uninfected individuals, it does support the importance of screening for diabetes in African populations infected with HIV where diabetes incidence appears to be high. Furthermore, these findings reinforce the importance of managing and screening for metabolic disease, such as diabetes as part of routine clinical care of patients infected with HIV in order to support continuity of care[44].

It is important to note that since none of the included studies were randomised, and there were too few studies for subgroup analyses, we cannot account for differences in disease course or lifestyle factors that confound exposure to cART or diabetes risk. Similarly, differences in cART exposure may be associated with regression or cure of illnesses in HIV, or with increased risk factors for diabetes. The mean age of included participants was generally lower than 45 years, which may have influenced the cumulative incidence reported in this review, since age influences diabetic progression. There was also heterogeneity in the method of diagnosis of diabetes between studies, which could have confounded results. Although all of the diagnosis methods included in this systematic review were well recognized (see Table 4), future diabetes screening programmes should strive to utilise gold standard diagnosis methods such as OGTT or HbA1c values[14]. The findings of this systematic review are further limited by the high risk of bias of included studies, largely due to confounding factors and limited blinding. Furthermore, the small sample size of included studies, as well as small number of studies available limit the conclusions that can be drawn. These limitations highlight the need for larger studies to be conducted examining diabetes incidence and prevalence in people with HIV in Africa, with focus on careful blinding and consideration of confounders.

In conclusion, this meta-analysis shows no significant association between HIV infection or treatment and diabetes prevalence in African population studies. Furthermore, incidence of diabetes in Africa in HIV infected patients on cART is no greater than in a normal ageing population, yet is higher than incidence rates in HIV infected individuals outside of Africa. Larger case control studies with effective blinding and consideration of confounders need to be conducted in Africa in order to further elucidate these associations in comparison to international findings. Currently, HIV infection and cART do not seem to predispose patients in Africa to diabetes, however high incidence rates warrant focus on screening and preventative programmes for HIV infected people living in Africa.

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CONTRIBUTION STATEMENT

AP contributed to conception and design; acquired, analysed and interpreted the data; drafted the article, and approved the final version for publication. RJM acquired the data, revised the article and approved the final version for publication. LS acquired the data, revised the article and approved the final version for publication. JAG acquired the data, revised the article and approved the final version for publication. LKM acquired the data, revised the article and approved the final version for publication. DMA acquired the data, revised the article and approved the final version for publication. SAN contributed to conception and design, acquired and interpreted the data, revised the article and approved the final version for publication. We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

DATA SHARING

No additional data available

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FIGURE LEGENDS

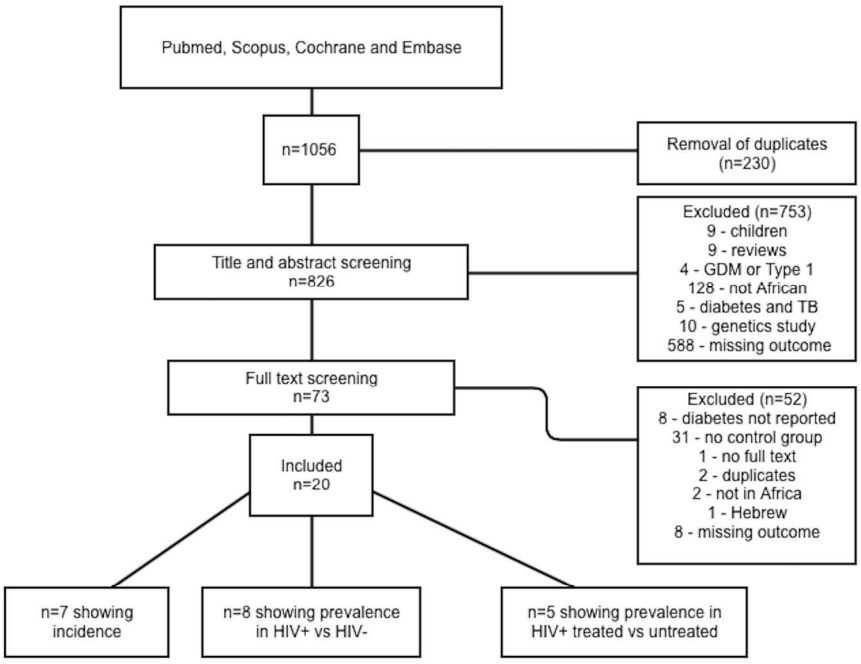
Figure 1. Flow diagram of article selection process, and reasons for inclusion and exclusion

Figure 2. Risk of bias assessment for studies included in the analysis

Figure 3. Incidence rates of diabetes in HIV infected and treated participants in Africa

Figure 4. Meta-analysis of studies comparing diabetes in HIV-infected and HIV-uninfected participants.

Figure 5. Meta-analysis of studies comparing diabetes in HIV-infected treated and untreated participants.



Flow diagram of article selection process, and reasons for inclusion and exclusion

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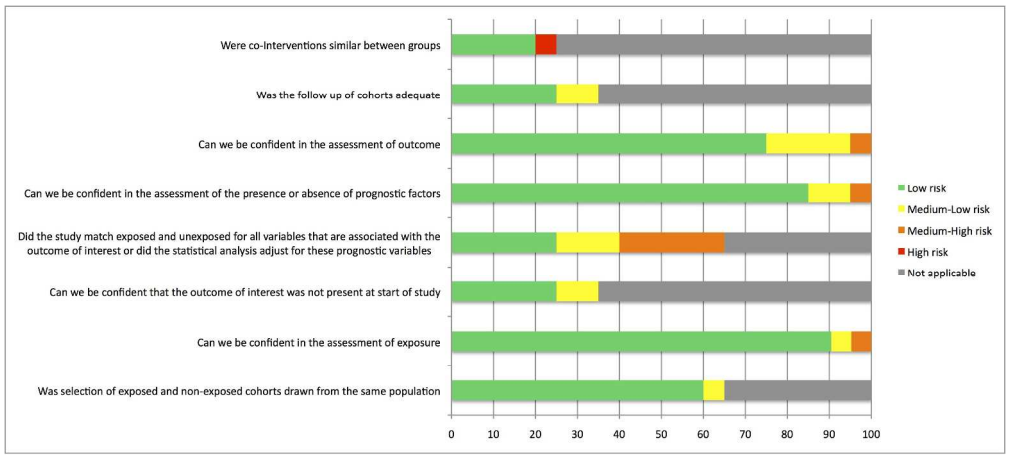

Risk of bias assessment for studies included in the analysis

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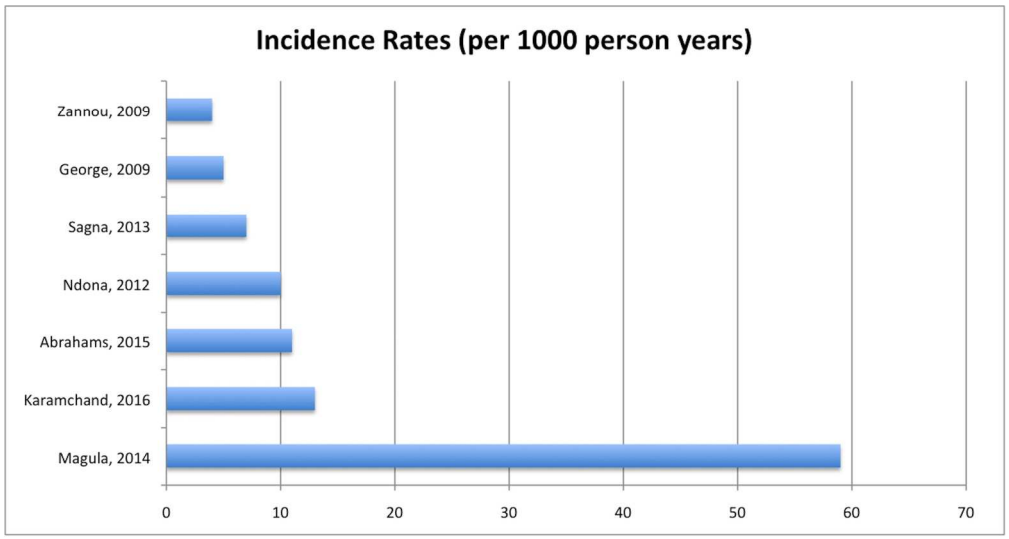

Incidence rates of diabetes in HIV infected and treated participants in Africa

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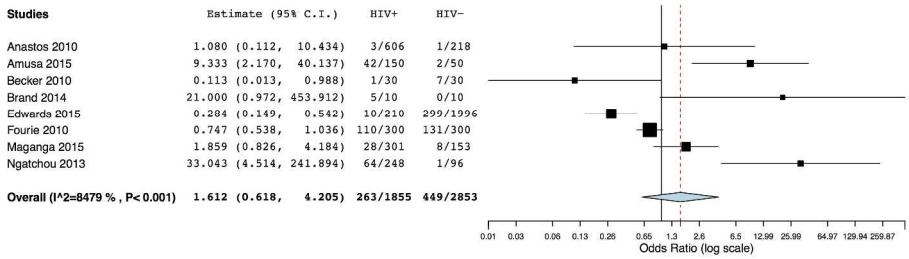

Meta-analysis of studies comparing diabetes in HIV-infected and HIV-uninfected participants.

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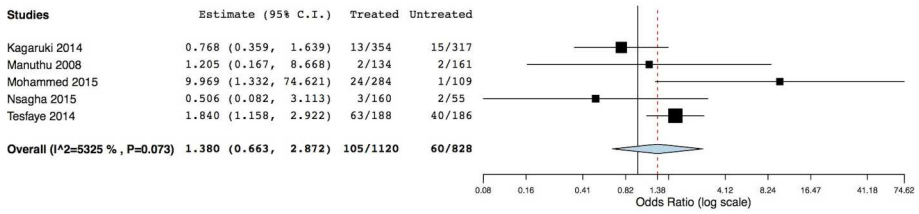

Meta-analysis of studies comparing diabetes in HIV-infected treated and untreated participants.

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AND
(diabetes:ab,ti OR 'diabetes mellitus':ab,ti OR diabetic:ab,ti OR 'impaired glucose control':ab,ti OR 'impaired glucose uptake':ab,ti OR 'impaired glucose tolerance':ab,ti OR 'glucose intolerance':ab,ti OR 'glucose tolerance':ab,ti OR 'glucose metabolism':ab,ti OR 'hyperglycaemia':ab,ti OR 'hyperglycemia':ab,ti OR 'hyperglycaemia':ab,ti OR 'glucose plasma':ab,ti OR 'plasma glucose':ab,ti OR 'blood glucose':ab,ti OR 'insulin resistance':ab,ti OR 'insulin sensitivity':ab,ti OR 'glucose tolerance test':ab,ti OR 'oral glucose tolerance':ab,ti OR 'ogtt':ab,ti OR 'intravenous glucose tolerance':ab,ti OR 'glucose day curve':ab,ti NOT 'type 1':ab,ti OR 'diabetes mellitus'/exp OR 'hyperglycemia'/exp OR 'glucose tolerance test'/exp OR 'insulin resistance'/exp)
AND
('Africa':ab,ti OR African:ab,ti OR Algeria:ab,ti OR Angola:ab,ti OR Benin:ab,ti OR Botswana:ab,ti OR 'Burkina Faso':ab,ti OR Burundi:ab,ti OR 'Cabo Verde':ab,ti OR Cameroon:ab,ti OR 'Central African Republic':ab,ti OR Chad:ab,ti OR Comoros:ab,ti OR 'Congo, Republic of the':ab,ti OR 'Congo, Democratic Republic of the':ab,ti OR 'Cote dIvoire':ab,ti OR Djibouti:ab,ti OR Egypt:ab,ti OR 'Equatorial Guinea':ab,ti OR Eritrea:ab,ti OR Ethiopia:ab,ti OR Gabon:ab,ti OR Gambia:ab,ti OR Ghana:ab,ti OR Guinea:ab,ti OR 'Guinea-Bissau':ab,ti OR Kenya:ab,ti OR Lesotho:ab,ti OR Liberia:ab,ti OR Libya:ab,ti OR Madagascar:ab,ti OR Malawi:ab,ti OR Mali:ab,ti OR Mauritania:ab,ti OR Mauritius:ab,ti OR Morocco:ab,ti OR Mozambique:ab,ti OR Namibia:ab,ti OR Niger:ab,ti OR Nigeria:ab,ti OR Rwanda:ab,ti OR 'Sao Tome and Principe':ab,ti OR Senegal:ab,ti OR Seychelles:ab,ti OR 'Sierra Leone':ab,ti OR Somalia:ab,ti OR 'South Africa':ab,ti OR 'South Sudan':ab,ti OR Sudan:ab,ti OR Swaziland:ab,ti OR Tanzania:ab,ti OR Togo:ab,ti OR Tunisia:ab,ti OR Uganda:ab,ti OR Zambia:ab,ti OR Zimbabwe:ab,ti OR 'Ivory Coast':ab,ti OR 'Africa'/exp OR 'African'/exp))

OR

((haart:ab,ti OR 'highly active anti retroviral therapy':ab,ti OR 'highly active anti retroviral therapies':ab,ti OR 'highly active anti-retroviral therapy':ab,ti OR 'highly active anti-retroviral therapies':ab,ti OR 'highly active antiretroviral therapy':ab,ti OR 'highly active antiretroviral therapies':ab,ti OR 'anti retroviral therapy':ab,ti OR 'antiretroviral therapy':ab,ti OR 'anti retroviral therapies':ab,ti OR 'antiretroviral therapies':ab,ti OR 'anti-retroviral therapy':ab,ti OR 'anti-retroviral therapies':ab,ti OR 'protease inhibitor':ab,ti OR 'protease antagonist':ab,ti OR antiprotease:ab,ti OR 'hiv protease inhibitor':ab,ti OR 'hiv antiprotease':ab,ti OR 'hiv protease antagonist':ab,ti OR 'peptidase inhibitor':ab,ti OR 'endopeptidase inhibitor':ab,ti OR 'reverse transcriptase inhibitor':ab,ti OR 'reverse-transcriptase inhibitor':ab,ti OR 'antiviral agent':ab,ti OR antiviral:ab,ti OR 'antiviral drug':ab,ti OR 'agent, anti-retroviral':ab,ti OR 'anti retroviral agent':ab,ti OR 'antiretroviral agent':ab,ti OR 'fusion inhibitor, hiv':ab,ti OR 'hiv cell fusion inhibitor':ab,ti OR 'hiv entry inhibitor':ab,ti OR 'hiv integrase inhibitor':ab,ti OR 'hiv integrase inhibitors':ab,ti OR 'ccr5 receptor antagonist':ab,ti OR 'highly active antiretroviral therapy'/exp)
AND
(diabetes:ab,ti OR 'diabetes mellitus':ab,ti OR diabetic:ab,ti OR 'impaired glucose control':ab,ti OR 'impaired glucose uptake':ab,ti OR 'impaired glucose tolerance':ab,ti OR 'glucose intolerance':ab,ti OR 'glucose tolerance':ab,ti OR 'glucose metabolism':ab,ti OR 'hyperglycaemia':ab,ti OR 'hyperglycemia':ab,ti OR 'hyperglycaemia':ab,ti OR 'glucose plasma':ab,ti OR 'plasma glucose':ab,ti OR 'blood glucose':ab,ti OR 'insulin resistance':ab,ti OR 'insulin sensitivity':ab,ti OR 'glucose tolerance test':ab,ti OR 'oral glucose tolerance':ab,ti OR 'ogtt':ab,ti OR 'intravenous glucose tolerance':ab,ti OR 'glucose day curve':ab,ti NOT 'type 1':ab,ti OR 'diabetes mellitus'/exp OR 'hyperglycemia'/exp OR 'glucose tolerance test'/exp OR 'insulin resistance'/exp)
AND
('Africa':ab,ti OR African:ab,ti OR Algeria:ab,ti OR Angola:ab,ti OR Benin:ab,ti OR Botswana:ab,ti OR 'Burkina Faso':ab,ti OR Burundi:ab,ti OR 'Cabo Verde':ab,ti OR Cameroon:ab,ti OR 'Central African Republic':ab,ti OR Chad:ab,ti OR Comoros:ab,ti OR 'Congo, Republic of the':ab,ti OR 'Congo, Democratic Republic of the':ab,ti OR 'Cote dIvoire':ab,ti OR Djibouti:ab,ti OR Egypt:ab,ti OR 'Equatorial Guinea':ab,ti OR Eritrea:ab,ti OR Ethiopia:ab,ti OR Gabon:ab,ti OR Gambia:ab,ti OR Ghana:ab,ti OR Guinea:ab,ti OR 'Guinea-Bissau':ab,ti OR Kenya:ab,ti OR Lesotho:ab,ti OR Liberia:ab,ti OR Libya:ab,ti OR Madagascar:ab,ti OR Malawi:ab,ti OR Mali:ab,ti OR Mauritania:ab,ti OR Mauritius:ab,ti OR Morocco:ab,ti OR Mozambique:ab,ti OR Namibia:ab,ti OR Niger:ab,ti OR Nigeria:ab,ti OR Rwanda:ab,ti OR 'Sao Tome and Principe':ab,ti OR Senegal:ab,ti OR Seychelles:ab,ti OR 'Sierra Leone':ab,ti OR Somalia:ab,ti OR 'South Africa':ab,ti OR 'South Sudan':ab,ti OR Sudan:ab,ti OR Swaziland:ab,ti OR Tanzania:ab,ti OR Togo:ab,ti OR Tunisia:ab,ti OR Uganda:ab,ti OR Zambia:ab,ti OR Zimbabwe:ab,ti OR 'Ivory Coast':ab,ti OR 'Africa'/exp OR 'African'/exp))

Filters: Published after Jan 01 2008, Human, Search field=title and abstract, Adolescent or adult (age>13years)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3,4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4,5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4,5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 5-6,Table 1-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 5, Figure 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 5-6,Table 1-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 5,6, Figure 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 5, Figure 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8-9

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Incidence and prevalence of Type 2 diabetes mellitus with HIV infection in Africa: A systematic review and meta analysis

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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Diabetes and endocrinology, Epidemiology, Public health
Keywords:	Type 2 diabetes mellitus, HIV, Africa, combination antiretroviral therapy, incidence, prevalence

Incidence and prevalence of Type 2 diabetes mellitus with HIV infection in Africa: A systematic review and meta analysis

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ABSTRACT

Objectives: This systematic review aims to investigate the incidence and prevalence of type 2 diabetes mellitus (T2DM) in HIV infected patients in African populations. **Setting:** Only studies reporting data from Africa were included. **Participants:** A systematic search was conducted using four databases for articles referring to HIV infection and antiretroviral therapy, and T2DM in Africa. Articles were excluded if they reported data on children, animals or type 1 diabetes exclusively. **Main outcome measures:** Incidence of T2DM and prevalence of T2DM. Risk ratios were generated for pooled data using random effects models. Bias was assessed using an adapted Cochrane Collaboration bias assessment tool. **Results:** Of 1056 references that were screened, only 20 were selected for inclusion. Seven reported the incidence of T2DM in HIV infected patients, eight reported the prevalence of T2DM in HIV infected vs uninfected individuals, and five reported prevalence of T2DM in HIV treated vs untreated patients. Incidence rates ranged from 4 to 59 per 1000 person years. Meta-analysis showed no significant differences between T2DM prevalence in HIV infected vs uninfected individuals (RR=1.61, 95% CI=0.62-4.21, p=0.33), or between HIV treated vs untreated patients (RR=1.38, 95% CI=0.66-2.87, p=0.39), and heterogeneity was high in both meta-analyses (I2=87% and 52% respectively). **Conclusion:** Meta-analysis showed no association between T2DM prevalence and HIV infection or ART, however these results are limited by the high heterogeneity of the included studies and moderate to high risk of bias, as well as, the small number of studies included. There is a need for well designed prospective longitudinal studies with larger population sizes to better assess incidence and prevalence of T2DM in African patients with HIV. Furthermore, screening for T2DM using gold standard methods in this population is necessary. **Trial Registration:** PROSPERO: 42016038689.

KEYWORDS

Type 2 diabetes mellitus, HIV, Africa, combination antiretroviral therapy, incidence, prevalence

STRENGTHS AND LIMITATIONS OF THE STUDY

- This is the first systematic review of the literature examining associations between HIV infection and treatment with type 2 diabetes mellitus incidence and prevalence in Africa.
- The stringent inclusion criteria used is a strength of this systematic review.
- Differences in methods of type 2 diabetes mellitus diagnosis across studies is a limitation.
- Heterogeneity and moderate to high risk of bias across studies is a limitation.
- The small number of studies meeting the inclusion criteria is a limitation.

BACKGROUND

The introduction of combination antiretroviral therapies (cARTs) in the treatment of human immunodeficiency virus (HIV) infection has resulted in significant extension of the predicted lifespan of HIV infected patients[1]. Consequently, patients with HIV are potentially at greater risk of developing non-communicable diseases (NCDs) than due to the ageing process alone; as the disease itself[2], and treatments used to combat HIV, are associated with metabolic complications[3].

Type 2 diabetes mellitus (T2DM) is one such disease that is becoming increasingly common, specifically in Africa due to rapidly transitioning lifestyles. An estimated 12.1 million people were living with T2DM in Africa in 2010[4] and it is predicted that this will increase to 23.9 milllion by 2030. Besides associations with age, obesity, sex, and race[5]; recent studies have associated T2DM with HIV infection, and with cART[1, 3, 5]. The mechanisms underlying these associations are not fully elucidated, but may reflect chronic systemic inflammation in response to HIV infection despite treatment[6, 7], antiretroviral drug-induced mitochondrial dysfunction, lipodystrophy and comorbidities[5]. Conversely, some studies have shown a decreased incidence of T2DM in HIV infected compared to uninfected individuals[8, 9]. T2DM is associated with increased morbidity and mortality, an estimated 1.5 million deaths were attributed directly to T2DM in 2012[10], and the implications of HIV infection and treatment on the incidence of T2DM is therefore important to explore. The aim of this systematic review is to investigate the incidence of T2DM in HIV infected patients in Africa, as well as, the prevalence of T2DM in HIV infected and cART treated patients in comparison to non infected and non treated individuals.

METHODS

The systematic review focused on the associations between HIV infection, ARV therapy and T2DM. This review was registered in the PROSPERO registry for systematic reviews (Registration number 42016038689)[11], and was conducted in accordance with the PRISMA guidelines[12].

Search Strategy

The search for this systematic review was conducted in May 2016 and included terms in the determinants of HIV infection and antiretroviral therapy, the domain of Africa, and the outcome of T2DM. Restrictions included age (>13 years), date of publication (after January 01 2008 due to the presence of an existing review examining prevalence of T2DM in HIV conducted in 2008[13]). The title and abstracts of articles in Pubmed, Scopus, the Cochrane library, and Embase were searched; and a sample of the Embase search strategy is available online as a supplementary file. Keywords used included: 'HIV', 'diabetes', 'Africa', and 'antiretroviral therapy'.

Study Selection

All observational studies (cohort, case-control, and cross-sectional) that assessed the relationship between HIV seropositivity with or without cART therapy, and T2DM in Africa were included. Animal studies, biomolecular studies, studies not written in English or French, case reports, and secondary analyses, were excluded. Studies reporting outcomes in children or pregnant women, or reporting type 1 diabetes outcomes only, or not reporting T2DM incidence or prevalence (but hyperglycemia or impaired glucose tolerance for example) were also excluded. Studies that did not report prevalence of T2DM in HIV infected compared to HIV uninfected participants; or prevalence of T2DM between cART exposure compared to untreated HIV infected patients; or incidence of T2DM in HIV infected patients were excluded. Authors of individual studies defined the criteria for T2DM diagnoses, and variant criteria were included provided diagnosis was made using a recognised score for a fasted blood glucose, or an oral glucose tolerance test (OGTT), or HbA1c values[14].

Screening and data extraction

Two independent reviewers (AP, RJM) independently screened all articles retrieved by the search strategy by title and abstract for eligibility according to inclusion and exclusion criteria. Any discrepancies between the two reviewers were discussed and consensus was reached. The full text was accessed if necessary for further clarification. Full texts of eligible articles were then retrieved and divided amongst all reviewers. If no full text was available, one attempt was made to contact the author. Each full text was assessed for eligibility by one reviewer, and a second reviewer was available for consultation. Data extraction was then performed using a standardised data extraction form. One reviewer (AP) reassessed data extraction for all eligible full texts. Data of interest was study design, study setting and country, population, age, body mass index (BMI), number of patients included in each group, control population, cART treatment at the time of inclusion, duration of cART treatment, method of T2DM diagnosis, incidence of known risk factors for T2DM such as obesity, treatment provided for T2DM, incidence of T2DM in the control group and group with HIV and/or antiretroviral therapy, when applicable OR/RR, and follow-up duration. In cases of incomplete data, one attempt was made to contact the corresponding author by email and if no response was received the paper was excluded.

Data synthesis

Three separate analyses were performed for articles that examined incidence of T2DM; prevalence of T2DM in HIV infected vs uninfected participants; and prevalence of T2DM in HIV infected and treated vs untreated participants. Meta-analysis was conducted for articles with sufficiently homogenous outcome measures and study designs. The principle summary measure used was risk ratio (RR), and in cases of substantial heterogeneity (I2>50%) according to the Cochrane handbook[15], a binary random effects model (using the DerSimonian-Laird method) was applied. Analyses were conducted using OpenMetaAnalyst. A priori subgroup analyses based on geographical localisation, age, ART medication/treatment strategy and duration, severity of HIV, and method of

T2DM diagnosis were not possible due to insignificant sub categorisation of data and insufficient number of included studies[15].

Risk of bias assessment

Studies were assessed for risk of bias using the Evidence Partner's risk of bias tool for cohort studies[16] as 'low risk', 'medium-low risk', 'medium-high risk', 'high risk', or 'not applicable' for the categories of: similarity of intervention, adequacy of follow up, assessment of outcome, assessment of prognostic factors, matching relevant variables between case and control, presence of outcome of interest at start of the study, assessment of exposure, and selection of populations. This tool is available as a supplementary file.

RESULTS

The search provided 1056 results. After screening, 20 articles met the eligibility criteria[17-36] and were included in the analysis (Figure 1). Of these, 7[17-23] articles reported incidence of T2DM in HIV infected participants, 8[24-31] reported prevalence of T2DM in HIV infected participants compared to uninfected controls, and 5[32-36] reported prevalence of T2DM in HIV infected participants on treatment compared to untreated controls. In included studies, T2DM was diagnosed if participants were being treated for T2DM, or by oral glucose tolerance test (OGTT). As summarised in Table 1, four main criteria were used: World Health Organisation (WHO), American Diabetes Association (ADA), International Diabetes Federation (IDF), and National Cholesterol Education Programme (NCEP) criteria.

Table 1. Overview of diagnostic criteria used in the included studies

Criteria used	Definitions
WHO	Fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl).
ADA	Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) or 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during OGTT (75g) or A1C ≥6.5% (48 mmol/mol) or Random plasma glucose ≥200 mg/dL (11.1 mmol/L)
NCEP cut offs	Fasting plasma glucose ≥5.6 mmol/L
IDF	FPG ≥ 100 mg/dl (5.6 mmol/L)

WHO – world health organisation, ADA – American diabetes association, OGTT – oral glucose tolerance test, A1C - NCEP - National Cholesterol Education Programme, IDF – International diabetes federation

Risk of bias

A summary of the risk of bias assessment is presented in Figure 2. All included studies were observational, and 15 (71%) were case control studies. In 5% of studies there was a high risk of bias due to HIV treatment not being stated. In 25% of studies there was a medium-high risk of bias due to confounding variables. Four (20%) of studies had medium-low risk of bias due to T2DM diagnosis criteria. Three (14%) included studies were published conference proceedings.

Incidence of T2DM in HIV infected participants

Seven studies reported T2DM incidence in HIV infected participants (n=57006; Table 2). One of the included studies compared incidence in treated vs untreated participants[21], and another compared incidence in infected vs uninfected participants[20]. The rest of the studies assessed incidence in HIV infected and treated participants with no control group. Most participants were on cART, except for participants in the Sagna et al study who were on first line therapy, which was not clearly specified[22]. Mean age of participants ranged from 33.5 years[17] to 38 years [19, 23](age was not stated by Magula et al[20]). Mean BMI ranged from 19.2kg/m^2[23] to 27.9kg/m^2[17], and was not stated in one of the studies[20]. Mean duration of follow up ranged from 1.56 years[19] to 5.5 years[17], and the total number of participants followed up to completion was n=56875. The majority of participants were female in all studies where sex was stated. Incidence of T2DM was reported as absolute incidence, cumulative incidence, incidence proportion, and incidence rate per 1000 person years. Incidence rates ranged from 4[23] to 59[20], Figure 3. The combined incidence rate for all the included studies over 89640 person years of follow up was 17.4.

Author, Year	Setting	Population	Case	Control	ART	Follow up Mean/median	Diagnosis of T2DM	Prevalence at Baseline n(%)	Prevalence at follow-up n(%)	Cumulative Incidence	Incidence Proportion	Incidence Rate (per 1000 person years)	p-value

Abrahams, 2015	South Africa	103 women Mean age =33.5 Mean BMI=27.9	NA	NA	Stavudine/lamivudine	5.5 years n=94	ADA criteria	1 (1.0)	7 (7.5)	6.5%	5.83%	11	0.07
George, 2009	South Africa	42 black participants, 65% female mean age=34.4 mean BMI=22.7	NA	NA	Stavudine/Zidovudine	2 years n=42	NCEP cut off	1(2.4)	1(2.5)	0.1%	0.001 %	5	>0.05
Karamchand, 2016	South Africa	56298 participants, 64% female Mean age=38.14 Mean BMI=25.95	NA	NA	First line NNRTI regimen containing efavirenz or nevirapine	1.56 years n=56298	Prescription of anti-diabetic medication	0(0)	1500 (2.66)	2.66%	2.66%	13	Not reported
Magula, 2014	South Africa	238 participants	n=150 treated	n=88 uninfected	Initiated - tenofovir, lamivu- dine, efavirenz/nevirapine	2 years n=150	WHO criteria	0(0)	13(8.66)	8.66%	8.66%	59	Not reported
Ndona, 2012	DRC	102 participants, 51% female, mean age= 43.4 mean BMI=23.1	n=49 HIV+ treated	n=53 HIV+ untreated	stavudine + lamivudine, zidovudine + lamivudine + nevirapine, or efavirenz	4 years n=102	WHO criteria	Not stated	5(4.9)	4.9%	4.9%	10	0.06
Sagna, 2013	Burkino Faso	144 participants, Mean age=37	NA	NA	Not stated (first line therapy)	3 years n=128	Not stated	Not stated	3(2.3)	2.3%	2.1%	7	Not reported
Zannou,	Benin	79	NA	NA	All started	2 years	WHO	0(0)	6(7.6)	7.6%	7.6%	4	Not

2009		participants, 59.5% female mean age= 38 mean BMI=19.2			combination therapy. Lamivudine + stavudine +efavirenz	n=61	criteria						reported

Table 2: Incidence Data

ART – anti retro-viral therapy, T2DM – type 2 diabetes mellitus, BMI – Body mass index, OGTT – oral glucose tolerance test, ADA – American Diabetes Association, NNRTI – non nucleotide reverse transcriptase inhibitors, WHO – world health organization, NCEP – National Cholesterol Education Programme, DRC – Democratic Republic of Congo, HIV – Human immunodeficiency virus

Prevalence of T2DM in HIV infected compared to uninfected participants

Table 3 shows the data for eight studies included in a meta-analysis comparing HIV infected (n=1715) to uninfected participants (n=2853). The majority of included participants were female, except for the study conducted by Brand et al[27], who only included males, and by Becker et al[26], where the majority of participants were male. In four of the included studies, infected participants were not on treatment[26, 27, 29, 31] and in a further two[24, 25], treatment was not stated. The remaining two studies examined participants on cART. Mean age ranged from 34.7 years[25] to 62 years[27] in uninfected participants and 37 years[30] to 47 years[27] in infected participants. Age was significantly different between the case and control groups in three studies[26-28]. Mean BMI ranged from 20.6kg/m^2 [25] to 28.1kg/m^2[31] in uninfected participants and from 21.1kg/m^2[25] to 25.1kg/m^2[31] in infected participants. BMI was significantly different between case and control groups in three studies[26, 27, 31]. A meta-analysis using a random effects model (I2=84.79%) indicated no significant association between HIV infection and T2DM prevalence (RR=1.61, 95% CI=0.62- 4.21, p=0.33), Figure 4.

Table 3: Prevalence Data: HIV infected (treated and untreated) vs non infected

Author, Year	Setting	Population	Case HIV+	Control HIV-	ART	Diagnosis	Prevalence case %	Prevalence control %	p-value
Amusa, 2015	Nigeria	200 adults	n=150, 62.6% female mean age=40.6	n=50, 60% female mean age=40.2	Not stated	FPG, criteria not stated	28.0	4.0	0.01
Anastos, 2010	Rwanda	824 women	n=606 mean age=42.4 mean BMI=21.1	n=218 mean age=34.7 Mean BMI=20.6	Not stated	Self report or WHO criteria	0.5	0.5	0.98
Becker, 2010	South Africa	60 adults	n=30, 33% female mean age=43 mean BMI=25	n=30, 40% female mean age=54 mean BMI=28	Not on treatment	Prescription of anti-diabetic medication or diagnosis upon admission	3.0	23.0	0.05
Brand, 2014	South Africa	20 black males requiring amputation	n=10 mean age=47 mean BMI=22.4	n=10 mean age=62 mean BMI=25.3	Not on treatment	WHO criteria or prescription of anti-diabetic medication	50.0	0.0	<0.05
Edwards, 2015	Kenya	2206 adults	n=210, 69% female mean	n=1996, 71% female	First line ART utilized tenofovir/lamivudin	WHO criteria	4.8	15.0	<0.01

			age=43	mean age=49	e/efavirenz; second line lopinavir/ritonavir instead of efavirenz				
Fourie, 2010	South Africa	600 adults	n=300, 61% female mean age=44 mean BMI=22.9	n=300, 61% female mean age=44 mean BMI=22.8	Not on treatment	IDF criteria	36.6	43.7	0.64
Maganga, 2015	Tanzania	454 adults	n=301, 67.8% female mean age=37 (untreated) and 40 (treated) mean BMI=22.0 (untreated) and 23.7(treated)	n=153, 61,4% female mean age=38 mean BMI=23.8	n=151 not on treatment n=150 on treatment - 21% on protease inhibitors (lopinavir and ritonavir); rest on other ART: nevirapine, efavirenz, tenofovir, stavudine, zidovudine	WHO criteria	9.3	5.2	0.04 (untreated vs control) and 0.001 (treated vs control)
Ngatchou, 2013	Cameroon	204 adults	n=108, 74% female mean age=39 mean BMI=25.1	n=96, 72% female mean age =41 mean BMI=28.1	Not on treatment	WHO criteria	26.0	1.0	0.01

ART – anti retro-viral therapy, HIV – Human immunodeficiency virus, FPG – fasting plasma glucose, BMI – Body mass index, WHO – world health organization, IDF – International diabetes federation

Prevalence of T2DM in HIV infected treated compared to untreated participants

Table 4 shows the data for five studies included in the meta-analysis comparing HIV treated (n=1120) to untreated participants (n=828). The majority of included participants were female (range 58%[34] to 75% female[36]), and mean age ranged from 32.7 years[33] to 44.2 years[36] (age was not stated for Manuthu et al[34]). All treated participants were receiving cART (therapy not stated by Kagaruki et al[32]). Where stated, age was higher in treated compared to untreated participants[32, 33, 36], yet significance was not stated for these age differences. Mean BMI was only reported in two studies, and was in the WHO healthy weight category (22kg/m^2) for both groups in one study[33], and in the WHO overweight category (26.5kg/m^2) for both groups in the second study[36]. A meta-analysis using a random effects model (I2=53.25%) indicated no significant association between HIV treatment and T2DM prevalence (RR=1.38, 95% CI=0.66- 2.87, p=0.39), Figure 5.

Table 4: Prevalence Data: HIV infected treated vs untreated

Author, Year	Setting	Population	Case Treated	Control Untreated	ART	Diagnosis	Prevalence Case %	Prevalence Control %	p-value
Kagaruki, 2014	Tanzania	671 participants, 70.5% female mean age=38.7	n=354, 67.8% female mean age=40.6	n=317, 73.5% female mean age=36.7	Not stated	WHO criteria	3.7	4.7	Not stated
Manuthu, 2008	Kenya	295 participants, 58% female	n=134	n=161	82.7% on d4t-based regimen, 51.1% on d4T+3TC+nevirapine 31.6% on d4T+3TC+efavirenz. 17.3% on AZT-based regimens 13.5% on AZT+3TC+efavirenz 3.8% on AZT+3TC+nevirapine; one PI-based regimen was AZT+3TC+lopinavir.	OGTT, criteria not stated	1.5	1.2	0.85
Mohammed, 2015	Ethiopia	393 adults, 66.9% female mean age=37.9	n=284	n=109	32.1% used the drug combination zidovudine + lamivudine + nevirapine	WHO criteria	8.5	0.9	<0.01
Nsagha, 2015	Cameroon	215 participants, 74.9% female Mean age 44.2 years Mean BMI=26.47	n=160, 77.5% female mean age=44.7 mean BMI=26.94	n=55, 67.3% female mean age=38.6 Mean BMI=25.09	AZT+3TC+efavirenx =1.3%, AZT+3TC+nevirapine =50%, TDF+3TC+efavirenz =27.5%, TDF+3TC+nevirapine= 13.1%, TDF+3TC+ lopinavir= 8.1%	WHO criteria	1.9	3.6	0.46

Tesfaye, 2014	Ethiopa	374 participants, 68% female Mean age=32.7	n=188, 63.8% female mean age=32.7 mean BMI=22.1	n=186, 68.8% female mean age=32.6 Mean BMI=22.2	58% on regimen containing efavirenz and 42% on nevirapine as NNRTI	IDF criteria	33.5	21.5	<0.05

ART – anti retro-viral therapy, WHO – world health organization, BMI – Body mass index, IDF – International diabetes federation, NNRTI – non nucleotide reverse transcriptase, d4t – stavudine, 3TC – lamivudine, , AZT - zidovudine, PI – protease inhibitor, OGTT – oral glucose tolerance test, TDF – tenofovir

DISCUSSION

This systematic review and meta-analysis of African studies showed no statistically significant association between HIV infection or cART exposure, and T2DM prevalence. This is contrary to study findings of international studies in Europe and North America that have shown a higher prevalence of T2DM in HIV infected compared to uninfected participants[37], particularly when treated with cART[1, 3, 5].

Incidence rates of T2DM in patients with HIV were described per 1000 person years of follow up and ranged considerably among the included studies. Cumulative incidence rate for the included studies was 17.4. For comparison, the incidence rate of T2DM in a healthy American population in 2012 was lower at 7.8[38]. Individually, three included papers reported lower incidence rates than the American population, and four reported higher incidence rates. There were no obvious differences between these studies in terms of age, sex, and duration of follow up, BMI or treatment; yet studies with larger sample sizes seemed to show higher incidence rates. A systematic review of T2DM in Sub-Saharan Africa[4] found only one study reporting an incidence rate of 29 in healthy adults (> 40 years) in Kinshasa[39]. In the present systematic review, only one included study on HIV infected participants reported higher incidence rates than the healthy adults in Kinshasa[20]. Therefore from the limited data available, and from the included studies in this systematic review it does not seem that incidence is higher in populations infected with HIV in Africa than in a healthy ageing African population.

T2DM incidence and prevalence rates have been reported internationally in HIV infected and treated patients. De Wit et al (2008) reported T2DM incidence rates of 6 (and an incidence rate of 4 for definite cases of T2DM) from the D:A:D study[40]. They examined 33 389 HIV infected patients from 212 clinics in Europe, USA, Argentina, and Australia, and found that treatment with stavudine increased the RR of T2DM by 1.19 per year of exposure (conversely, treatment with ritonavir and nevirapine decreased risk of T2DM). Interestingly, controlling for lipodystrophy did not modify this relationship, and a direct effect of treatment on mitochondrial toxicity was thus suggested. Baseline prevalence of T2DM in this study was 2.9%. Findings from the Multicentre AIDS cohort study (MACS) showed a T2DM incidence of 47 in HIV infected white males who were on cART vs 17 in those who were cART naïve, however this study used only a single increased fasting plasma glucose as their diagnostic criteria[41]. Nigatu et al, in 2013 conducted a systematic review looking at incidence of various comorbidities, including T2DM, with HIV infection, and found a combined T2DM incidence rate of 6 (with a range of 4.2-36) in a sample of 44 484 individuals[42]. In the studies included in their systematic review, ART exposure increased incidence rates when compared to ART naïve patients. Conversely, Tripathi et al (2014) found that 6816 HIV infected patients (of which over 80% were treated with ART) had lower T2DM incidence rates than matched, non-infected individuals (11.4 vs 13.6)[8]. Similarly, Nix et al in 2014 stated that their summary of the literature found a similar decreased incidence of T2DM in HIV infected individuals compared to controls[9]. The present systematic review

found a combined T2DM incidence rate of 17.4 in HIV infected cART treated African patients, which is higher than incidence rates found in all of the above-mentioned studies except for the males in the MACS study. Therefore, although incidence does not seem to be higher in HIV infected patients in Africa compared to a normal ageing population in Africa; T2DM incidence in HIV infected people in Africa does appear to be higher than rates reported internationally for HIV infected patients, and those reported for a healthy American population.

It is possible that the higher incidence of T2DM in African HIV infected individuals compared to international incidence data for HIV infected individuals could be explained by the high presence of risk factors for T2DM in African populations, regardless of HIV status. Although prevalence of T2DM in Africa is lower than other regions in the world, the IDF Diabetes atlas (7th edition) states that more than two thirds of people with diabates in Africa are undiagnosed, and that prevalence rates are expecetd to more than double in the next few years. This predicted increase is the highest of all regions worldwide, indicating the greatest increase in incidence rates. Furthermore, the IDF state that lack of prevalence data in Africa makes these estimates somewhat weak, and it is thus possible that prevalence in Africa is in fact higher than reported. As many African populations are undergoing rapid transitions, the toxic combination of early life undernutrition in utero and infancy, combined with excessive weight gain in later life may be contributing to increased T2DM susceptibility[43]. In fact, in studies included in this systematic review where mean BMI was reported, a substantial proportion of participants infected with HIV were overweight or obese. This presents a different picture to the undernourished HIV infected individual previously associated with Africa, and may explain a higher incidence of T2DM as an effect of lifestyle rather than an HIV disease related risk. Although this systematic review has not shown a higher prevalence of T2DM in HIV infected individuals compared to uninfected individuals, it does support the importance of screening for T2DM in African populations infected with HIV where T2DM incidence appears to be high. Furthermore, these findings reinforce the importance of managing and screening for metabolic disease, such as T2DM as part of routine clinical care of patients infected with HIV in order to support continuity of care[44].

It is important to note that since none of the included studies were randomised, and there were too few studies for subgroup analyses, we cannot account for differences in disease course or lifestyle factors that confound exposure to cART or T2DM risk. Similarly, differences in cART exposure may be associated with regression or cure of illnesses in HIV, or with increased risk factors for T2DM. The mean age of included participants was generally lower than 45 years, which may have influenced the cumulative incidence reported in this review, since age influences diabetic progression. There was also heterogeneity in the method of diagnosis of T2DM between studies, which could have confounded results. Although all of the diagnosis methods included in this systematic review were well recognized (see Table 4), future T2DM screening programmes should strive to utilise gold standard diagnosis methods such as OGTT or HbA1c values[14]. The findings of this systematic review are further limited by the high risk of bias of included studies, largely due to confounding factors and limited blinding.

Furthermore, the small sample size of included studies, as well as small number of studies available limit the conclusions that can be drawn. These limitations highlight the need for larger studies to be conducted examining T2DM incidence and prevalence in people with HIV in Africa, with focus on careful blinding and consideration of confounders.

In conclusion, this meta-analysis shows no significant association between HIV infection or treatment and T2DM prevalence in African population studies. Furthermore, incidence of T2DM in Africa in HIV infected patients on cART is no greater than in a normal ageing population, yet is higher than incidence rates in HIV infected individuals outside of Africa. Larger case control studies with effective blinding and consideration of confounders need to be conducted in Africa in order to further elucidate these associations in comparison to international findings. Currently, HIV infection and cART do not seem to predispose patients in Africa to T2DM, however high incidence rates warrant focus on screening and preventative programmes for HIV infected people living in Africa.

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CONTRIBUTION STATEMENT

AP contributed to conception and design; acquired, analysed and interpreted the data; drafted the article, and approved the final version for publication. RJM acquired the data, revised the article and approved the final version for publication. LS acquired the data, revised the article and approved the final version for publication. JAG acquired the data, revised the article and approved the final version for publication. LKM acquired the data, revised the article and approved the final version for publication. DMA acquired the data, revised the article and approved the final version for publication. SAN contributed to conception and design, acquired and interpreted the data, revised the article and approved the final version for publication. We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

DATA SHARING

No additional data available

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FIGURE LEGENDS

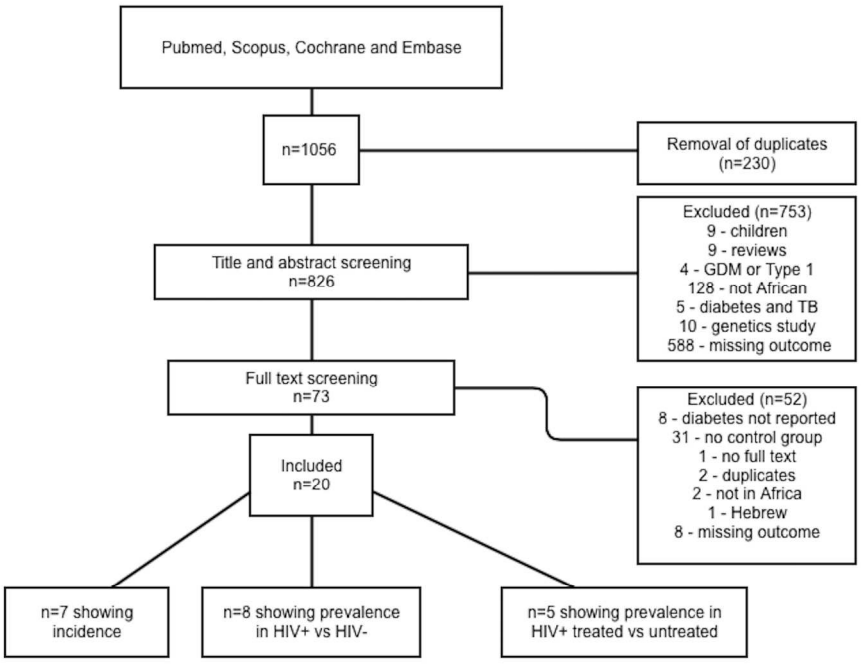
Figure 1. Flow diagram of article selection process, and reasons for inclusion and exclusion

Figure 2. Risk of bias assessment for studies included in the analysis

Figure 3. Incidence rates of T2DM in HIV infected and treated participants in Africa

Figure 4. Meta-analysis of studies comparing T2DM in HIV-infected and HIV-uninfected participants.

Figure 5. Meta-analysis of studies comparing T2DM in HIV-infected treated and untreated participants.



Flow diagram of article selection process, and reasons for inclusion and exclusion

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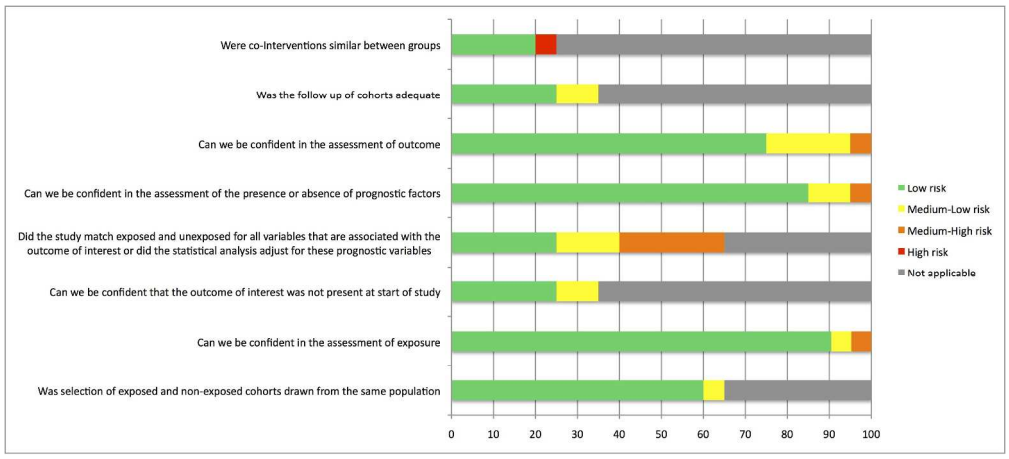

Risk of bias assessment for studies included in the analysis

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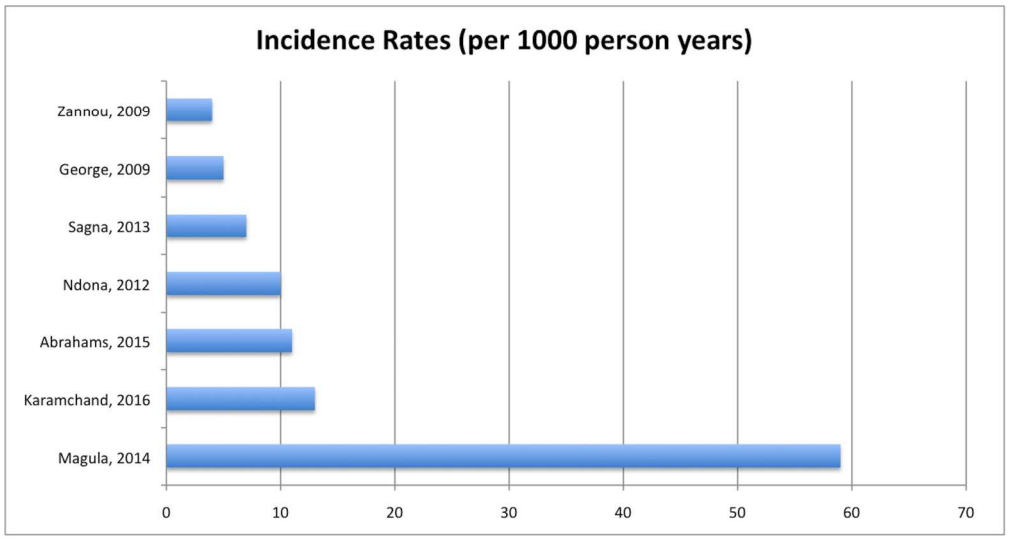

Incidence rates of diabetes in HIV infected and treated participants in Africa

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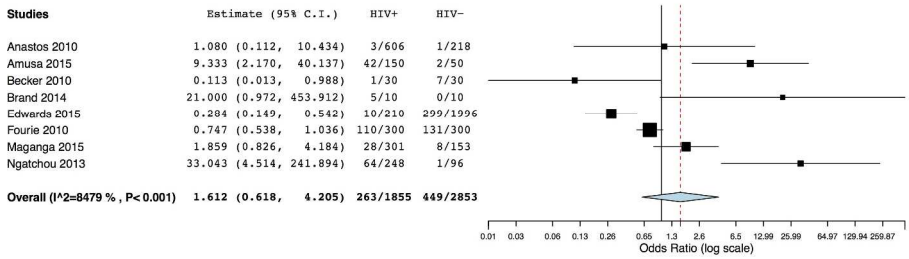

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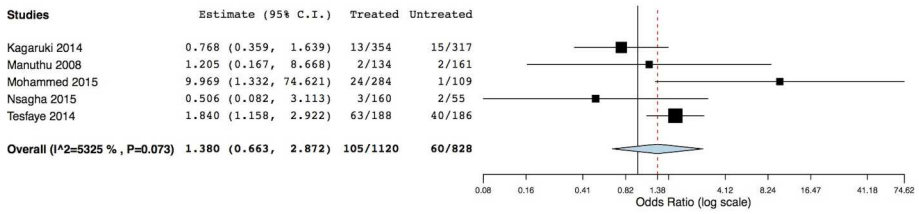

Meta-analysis of studies comparing diabetes in HIV-infected treated and untreated participants.

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AND
(diabetes:ab,ti OR 'diabetes mellitus':ab,ti OR diabetic:ab,ti OR 'impaired glucose control':ab,ti OR 'impaired glucose uptake':ab,ti OR 'impaired glucose tolerance':ab,ti OR 'glucose intolerance':ab,ti OR 'glucose tolerance':ab,ti OR 'glucose metabolism':ab,ti OR 'hyperglycaemia':ab,ti OR 'hyperglycemia':ab,ti OR 'hyperglycaemia':ab,ti OR 'glucose plasma':ab,ti OR 'plasma glucose':ab,ti OR 'blood glucose':ab,ti OR 'insulin resistance':ab,ti OR 'insulin sensitivity':ab,ti OR 'glucose tolerance test':ab,ti OR 'oral glucose tolerance':ab,ti OR 'ogtt':ab,ti OR 'intravenous glucose tolerance':ab,ti OR 'glucose day curve':ab,ti NOT 'type 1':ab,ti OR 'diabetes mellitus'/exp OR 'hyperglycemia'/exp OR 'glucose tolerance test'/exp OR 'insulin resistance'/exp)
AND
('Africa':ab,ti OR African:ab,ti OR Algeria:ab,ti OR Angola:ab,ti OR Benin:ab,ti OR Botswana:ab,ti OR 'Burkina Faso':ab,ti OR Burundi:ab,ti OR 'Cabo Verde':ab,ti OR Cameroon:ab,ti OR 'Central African Republic':ab,ti OR Chad:ab,ti OR Comoros:ab,ti OR 'Congo, Republic of the':ab,ti OR 'Congo, Democratic Republic of the':ab,ti OR 'Cote dIvoire':ab,ti OR Djibouti:ab,ti OR Egypt:ab,ti OR 'Equatorial Guinea':ab,ti OR Eritrea:ab,ti OR Ethiopia:ab,ti OR Gabon:ab,ti OR Gambia:ab,ti OR Ghana:ab,ti OR Guinea:ab,ti OR 'Guinea-Bissau':ab,ti OR Kenya:ab,ti OR Lesotho:ab,ti OR Liberia:ab,ti OR Libya:ab,ti OR Madagascar:ab,ti OR Malawi:ab,ti OR Mali:ab,ti OR Mauritania:ab,ti OR Mauritius:ab,ti OR Morocco:ab,ti OR Mozambique:ab,ti OR Namibia:ab,ti OR Niger:ab,ti OR Nigeria:ab,ti OR Rwanda:ab,ti OR 'Sao Tome and Principe':ab,ti OR Senegal:ab,ti OR Seychelles:ab,ti OR 'Sierra Leone':ab,ti OR Somalia:ab,ti OR 'South Africa':ab,ti OR 'South Sudan':ab,ti OR Sudan:ab,ti OR Swaziland:ab,ti OR Tanzania:ab,ti OR Togo:ab,ti OR Tunisia:ab,ti OR Uganda:ab,ti OR Zambia:ab,ti OR Zimbabwe:ab,ti OR 'Ivory Coast':ab,ti OR 'Africa'/exp OR 'African'/exp))

Filters: Published after Jan 01 2008, Human, Search field=title and abstract, Adolescent or adult (age>13years)

Tool to Assess Risk of Bias in Cohort Studies

1. **Was selection of exposed and non-exposed cohorts drawn from the same population?**

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Exposed and unexposed drawn for same administrative data base of patients presenting at same points of care over the same time frame

Examples of high risk of bias: exposed and unexposed presenting to different points of care or over a different time frame

2. Can we be confident in the assessment of exposure?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Secure record [e.g. surgical records, pharmacy records]; Repeated interview or other ascertainment asking about current use/exposure

Examples of higher risk of bias: Structured interview at a single point in time; Written self report; Individuals who are asked to retrospectively confirm their exposure status may be subject to recall bias – less likely to recall an exposure if they have not developed an adverse outcome, and more likely to recall an exposure (whether an exposure occurred or not) if they have developed an adverse outcome.

Examples of high risk of bias: uncertain how exposure information obtained

3. Can we be confident that the outcome of interest was not present at start of study

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?

Definitely yes (low risk of bias)	Mostly yes	Mostly no	Definitely no (high risk of bias)

Examples of low risk of bias: comprehensive matching or adjustment for all plausible prognostic variables

Examples of higher risk of bias: matching or adjustment for most plausible prognostic variables

Examples of high risk of bias: matching or adjustment for a minority of plausible prognostic variables, or no matching or adjustment at all. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

5. **Can we be confident in the assessment of the presence or absence of prognostic factors?**

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Interview of all participants; self-completed survey from all participants; review of charts with reproducibility demonstrated; from data base with documentation of accuracy of abstraction of prognostic data

Examples of higher risk of bias: Chart review without demonstration of reproducibility; data base with uncertain quality of abstraction of prognostic information

Examples of high risk of bias: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables

6. Can we be confident in the assessment of outcome?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Independent blind assessment; Record linkage; For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture.

Examples of higher risk of bias: Independent assessment unblinded; self-report; For some outcomes (e.g. vertebral fracture where reference to x-rays would be required) reference to the medical record would not be adequate outcomes.

Examples of high risk of bias: uncertain (no description)

7. Was the follow up of cohorts adequate?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring is unlikely to introduce bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a important impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is not large enough to have an important impact on the observed effect size; Missing data have been imputed using appropriate methods.

Examples of high risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is enough to induce important bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is large enough to induce clinically relevant bias in the observed effect size.

8. Were co-Interventions similar between groups?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Most or all relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed.

Examples of high risk of bias: Few or no relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3,4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4,5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4,5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 5-6,Table 1-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 5, Figure 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 5-6,Table 1-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 5,6, Figure 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 5, Figure 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8-9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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