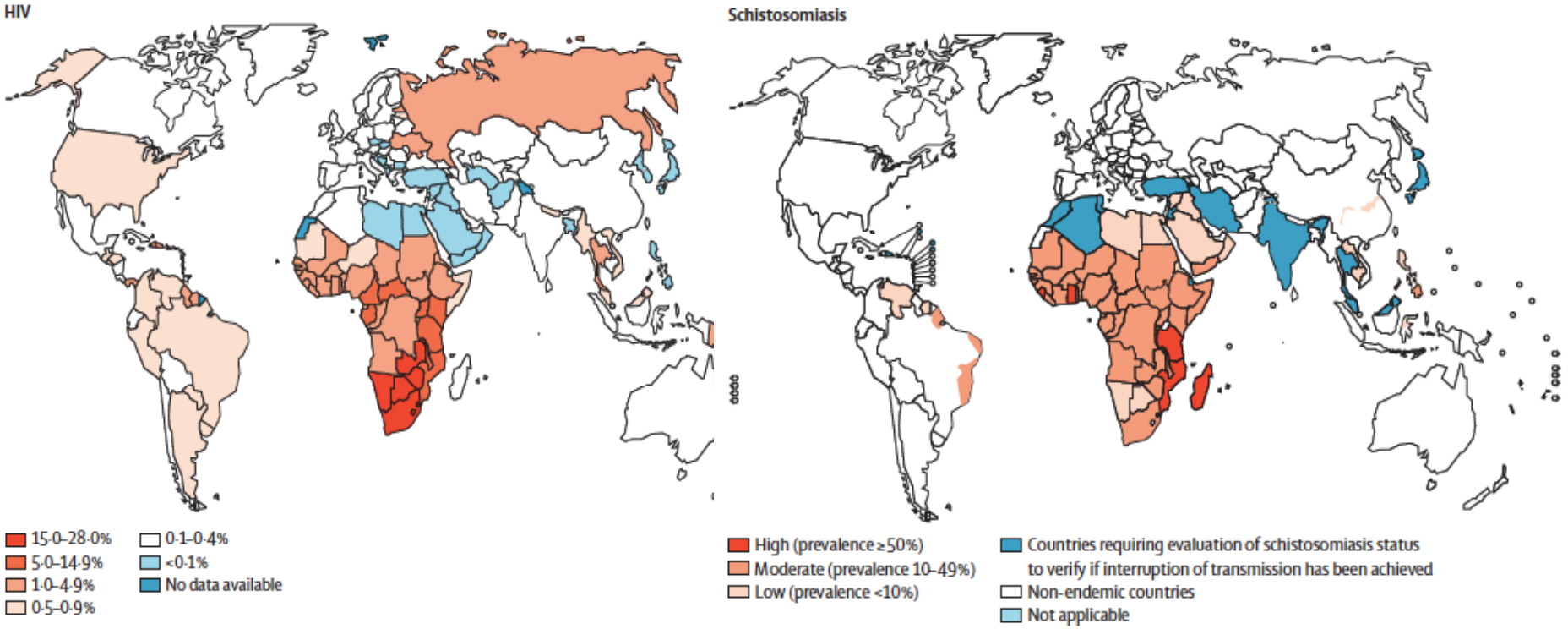
Female Genital Schistosomiasis a risk factor for HIV infection: a literature review

V.Christinet, MSF-UK
E. Comte, CIRES
Alexandra Calmy, HUG
Peter Odermatt, STPH
Daniel O'Brian, MSF-UK

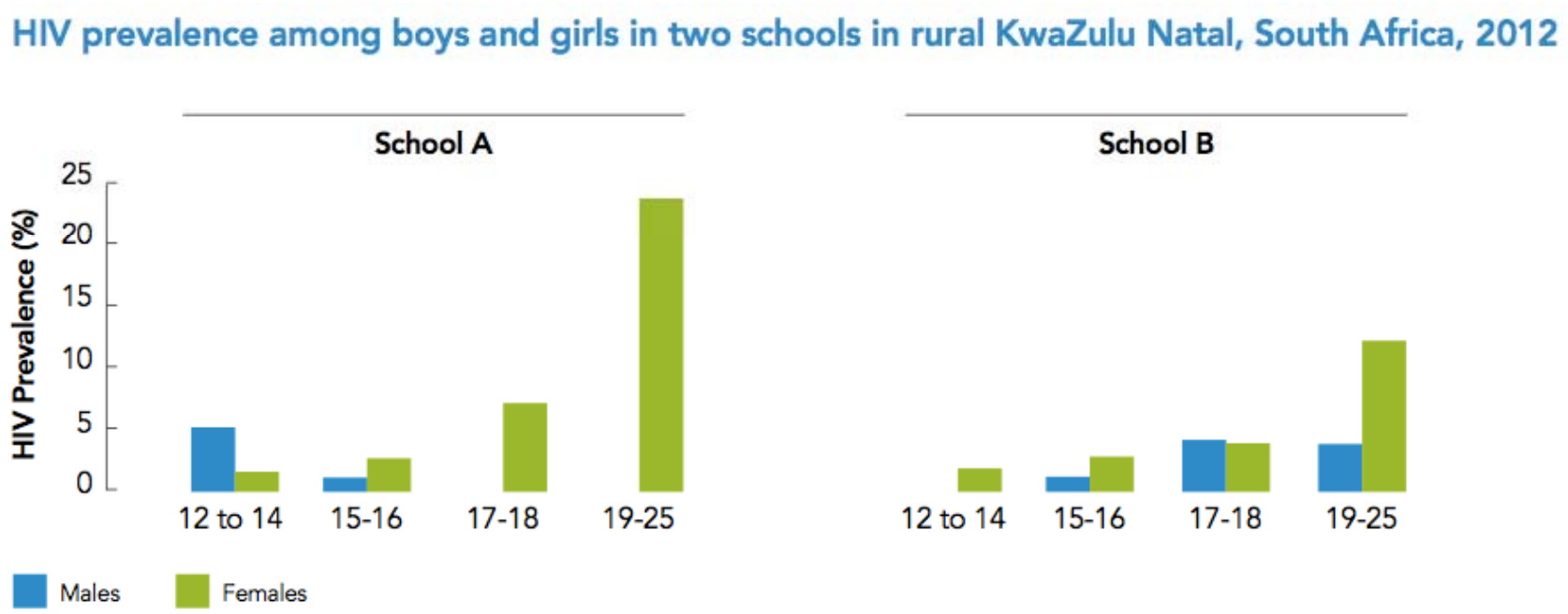
Epidemiological data: HIV and schistosomiasis prevalence



Bustinduy 2014

How do we explain such a high HIV incidence in young Sub-saharan African women

- 71% of the total HIV infection in sub-Saharan Africa, 58% are women (The Gap Report UNAIDS 2014)
- Only behavioural factors?
- Other vulnerability? Biological? Schistosomiasis?



Source: Kharsany, A.B., Mlotshwa, M., et al. (2012). HIV prevalence among high school learners - opportunities for school-based HIV-testing programmes and sexual reproductive health services. BMC Public Health 12: 231.

High HIV prevalence in young women in South Africa

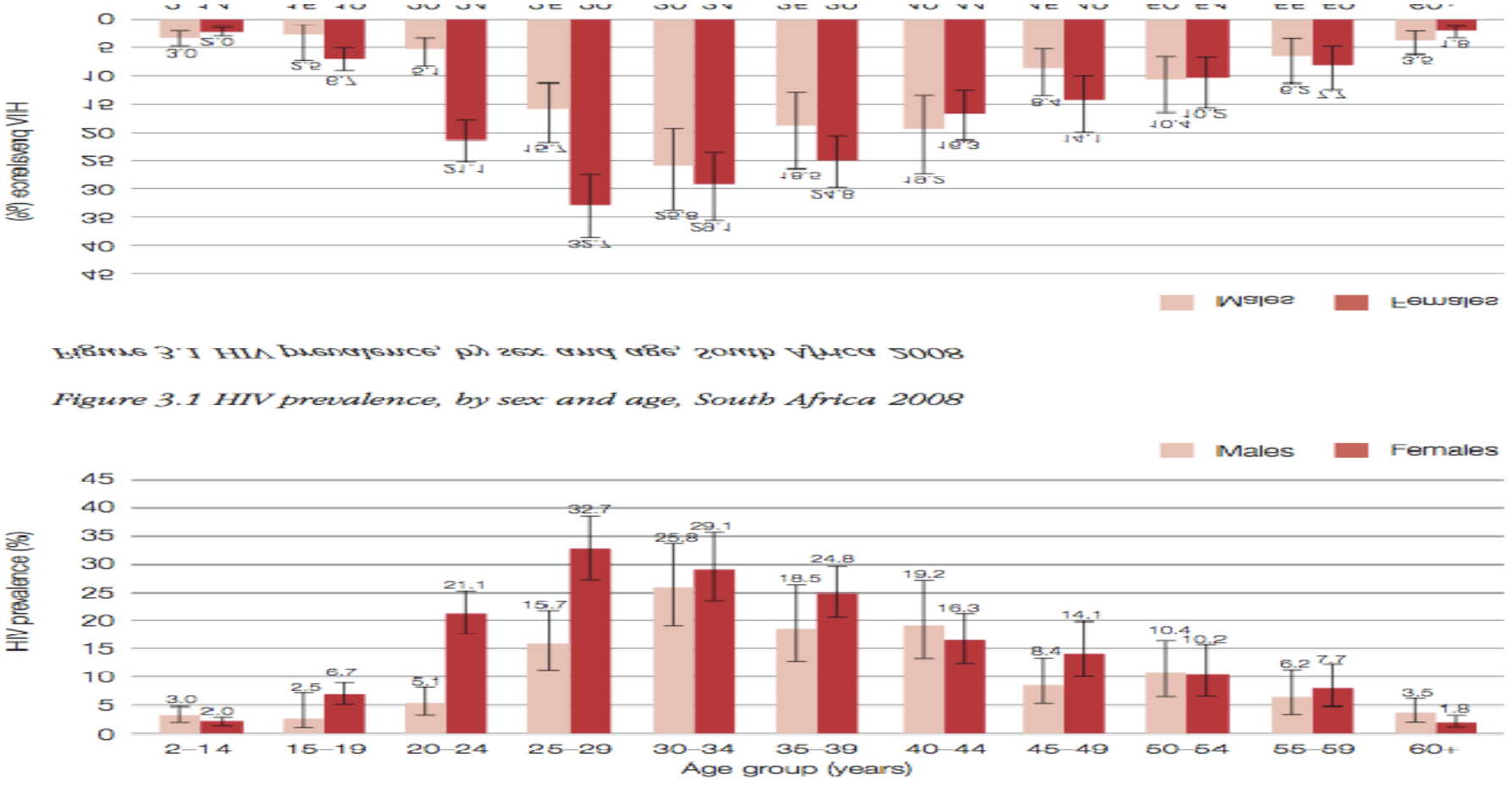


Figure 3.1 HIV prevalence, by sex and age, South Africa 2008

Shisana O (2009) South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2008.

Schistosoma hematobium and female genital schistosomiasis

FGS due to both species, **most frequently to S. hematobium** (litterature hemato>> mansoni)

S. haematobium 112 million cases in sub-Saharan Africa. Responsible for (Van der Werf 2003) :

- ohematuria (70 mio)
- omajor bladder wall pathology including bladder cancer (18 mio)
- omajor hydronephrosis leading to severe kidney damage (9.6 mio)

Estimated > 9-13 million women with FGS (Feldmeier 1995, Van des werf 2003), new estimate 20-150 million (Hotez 2014)

55-75% of women with urinary schistosomiasis have FGS (kjetland 1996, Leutscher 1997, Poggensee 1998)

Population based point prevalence FGS 33% - 75% (Madagascar, Tanzania, Malawi, Niger) (Poggensee 1999)

Female Genital Schistosomiasis

First case described and published in literature in 1899

Neglected manifestation of a neglected infection

Definition: presence of eggs and/ or a characteristic pathology in reproductive organs.

Lesions result from a complex delayed type hypersensitivity response to sequestered viable, dying or dead schisto eggs. (Poggensee 1999, 2001, Kjetland 2005)

cervix, vagina > upper genital tract (Gelfand 1958, Swai 2006)

Depending on the location (vulva, vagina, cervix, uterus, fallopian tubes, ovaries) FGS has been associated with:

- obleeding, discharge, pain, itching, genital ulceration, irregular menstruation, hypermenorrhea, spontaneous abortion (Leutscher 1998, Poggensee 2000, 2001 Swai 2006, kjetland 2005, Kjetland 2008,)
- ocancer, ectopic pregnancy and/or infertility, vesico-vaginal and recto-vaginal fistula (Feldmeier 1995, Poggensee 2001, Swai 2006, Kjetland 2006)

Can occur before puberty: genital symptoms associated with S. hematobium in girls from 10-12 yrs old (Hegertun 2013)

- .

Literature review

Hypothesis: Female genital schistosomiasis is a risk factor for HIV infection

The purpose of this literature review was to search for evidence that are compatible with this hypothesis

Method: search in pubmed with « mesh terms » and « all field » assoicating following keywords **hiv** or **acquired immunodeficiency syndrome** with **schistosomiasis** or **bilharzia** or **hematobium** keywords in pubmed, google scholar. Reference list from articles were scanned.

Results: 382 abstracts have been reviewed, 36 articles have been used for this presentation. References are presented grouped: biological/clinical data (7) and epidemiological data (6).

Discussion and conclusion

Biological plausibility of FGS increasing vulnerability to HIV

Breaks in the integrity of the mucosal barrier, due to either trauma or sexually transmitted ulcerative diseases associated with an increased risk of HIV transmission (Mabey 2000)

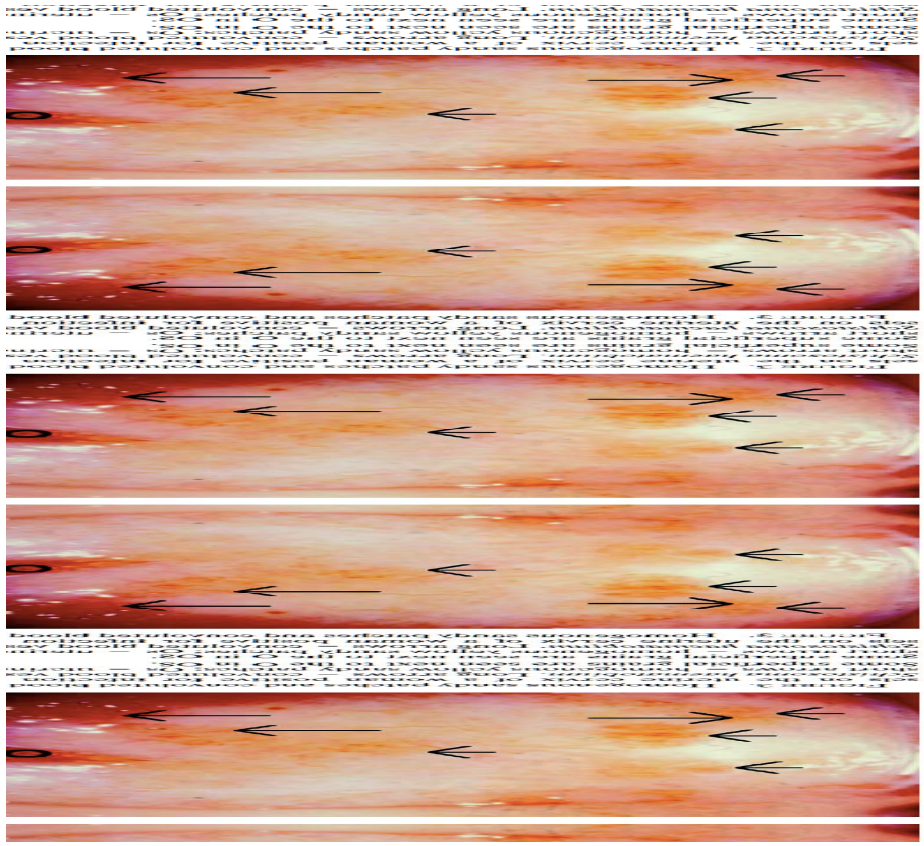
The cervix is the suggested site of most HIV acquisition, and the relative frequencies of the mucosal immune cells are crucial determinants of HIV transmission (Kaul 2008)

Schistosomiasis induced inflammatory process in the cervix associated with increased density of HIV target cells (CD4+ T cells, macrophages)(Jourdan 2011)

FGS was associated with a significantly higher frequency (Kleppa 2014):

- oCD14+ cells (monocytes) in blood (11.5% vs. 2.2%, p =

Break in the integrity of the mucosal barrier, neo-vascularisation, contact of pre-contact bleeding



Neovascularization contact bleeding associated with S.h.

Table 1. The association between *Schistosoma haematobium* and each of the four genital findings adjusted for HIV, length of stay in the area and age in 523 rural Zimbabwean women.

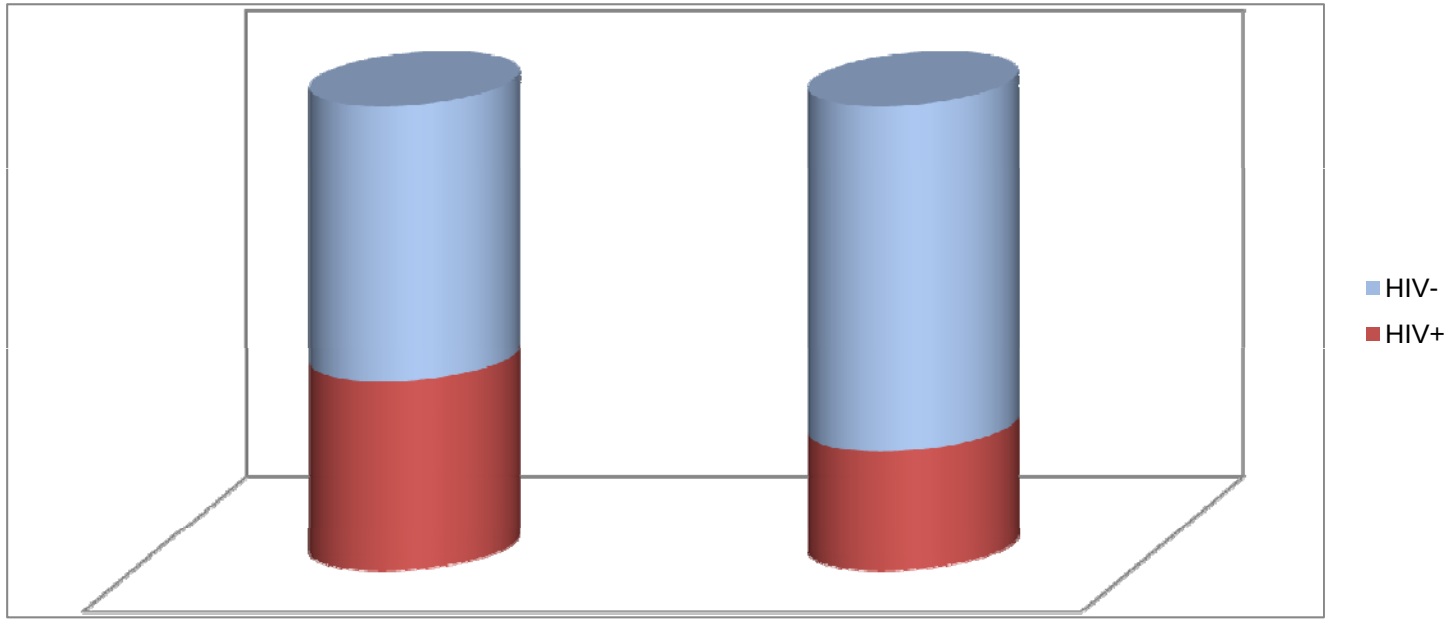
	S. haematobium ova in Pap smears[a]	
Genital mucosal finding[b]	Adjusted OR (95% CI)	*P*
Grainy sandy patches[c]	4.8 (2.1–10.9)	< 0.001
Homogenous yellow sandy patches[d]	2.8 (1.2–6.6)	0.019
Neo-vascularization[e]	5.1 (2.0–13.2)	0.001
Contact bleeding[f]	7.5 (1.8–31.6)	0.006

Kjetland 2006

S.h eggs in the genital tissue stongest predictor for neo-vascularization, contact bleeding and sandy patches in 527 rural Zimbabwean women/ multivariate analysis (Kjetland 2005)
125 biopsies from 111 tanzanien women with FGS: Main symptoms reported bleeding disorders (48%) (Swai 2006)
Increased cervicovaginal vascularity in association with S. haematobium eggs (Jourdan 2011, 2013)

FGS and HIV associated in a case-control study

In Zimbabwe 41% (29/70) HIV prevalence in women with **laboratory proven genital schistosomiasis** as opposed to 26% (96/375) HIV prevalence in the schistosomal eggs negative group (OR, 2.1; 95% CI, 1.2–3.5; P . 0.008) (Kjetland 2006)



Women follow-up and HIV seroconversion

7/224 women HIV seroconvert at 12 months
7/7 had FGS or urinary schistosomiasis (65% 142/217 in HIV negative women)(p=0.098)
Median age 28 yrs old (38 for HIV-negative women) (p=0.056)
6 married / 1 divorced
No STI differences between HIV seroconverters and HIV-negative women

Kjetland 2006

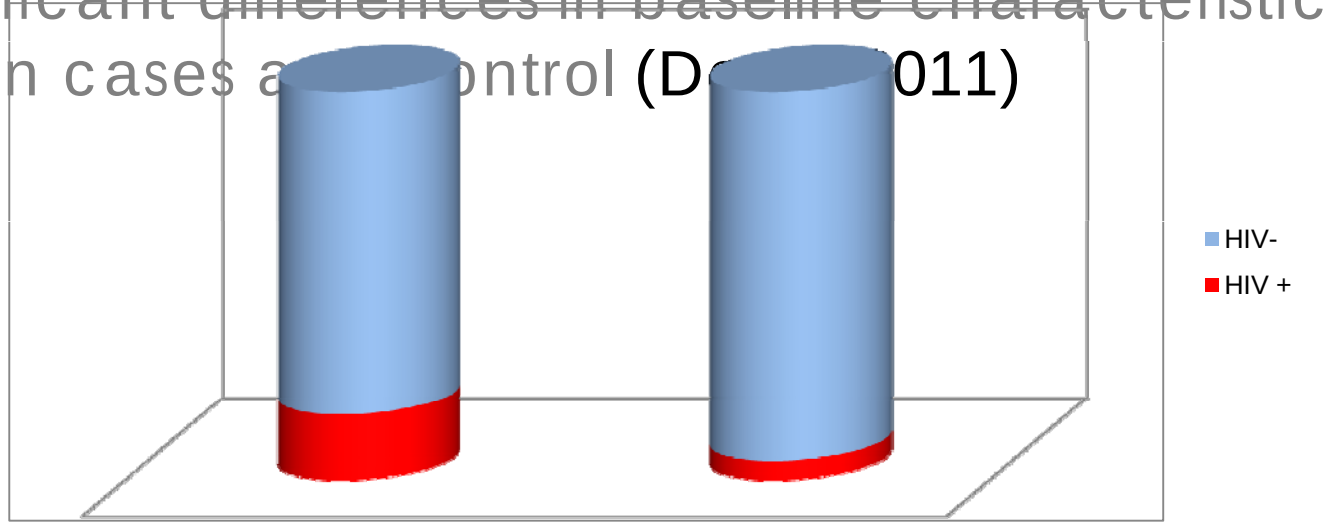
Female uro-genital and HIV schistosomiasis association

Case-control study in Tanzania

FUS (urinary or genital schistosomiasis incl 1 S. Mansoni) prevalence: 5% / HIV prevalence: 5.9%

HIV prevalence was 17% among women with FUS compared to 5.9% among controls (OR = 4.0, 95%; CI = 1.2–13.5 p=0.024)

No significant differences in baseline characteristics between cases and control (D 011)



HIV and S.hematobium prevalence correlation in sub-Saharan Africa

Ecological, regression, multivariate analysis
43 sub-Saharan African countries
Controlled for HIV specific risk factors and general health care indicators
HIV prevalence is associated to S. hematobium prevalence throughout sub-Saharan Africa
Each S. haematobium infection per 100 individuals was associated with a **2.9% (95% CI: 0.2–5.8%; p=0.038)** **relative increase in HIV** prevalence.

Ndeffo Mbah (2013)

Modelisation of HIV/AIDS & schisto codynamics

3 mathematical modelisation show a correlation show an impact of schistosomiasis on HIV/AIDS epidemic.
In these modelisation the treatement of schistosomiasis is effective in helping controlling HIV/AIDS epidemic (Mushayabasa 2010, Gibson 2010)
Annual praziquantel MDA in school age children in high risk communities could **reduce HIV incidence 9%** (95%CI: 3-22) **to 22%** (95%CI:18-42) after the first 20 years of intervention, depending on the country HIV prevalence (Model performed for Zambia, Angola, Kenya).
Extending the intervention to adults could further decrease HIV incidence and prevalence (Ndeffo Mbah 2014)

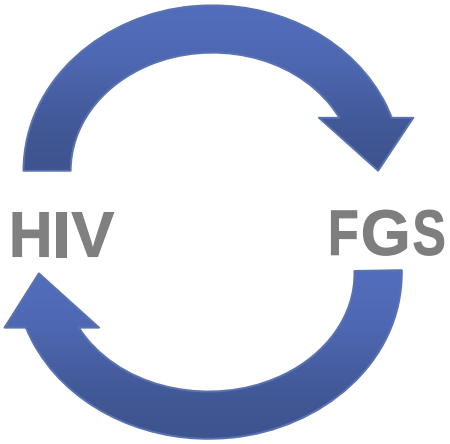
Urinary S.hematobium & HIV

- Urinary S.hematobium alone and HIV: no clear epidemiological association (N'Zoukoudi-N'Doundou 1995, Ndhlovu 2007, Thigpen 2011)
- Urinary S.hematobium eggs excretion decreased or is equivalent in HIV postive patients (N'Zoukoudi-N'Doundou 1995, Mwanakasale 2003, kallestrup 2005, Kleppa 2015)
- Urinary egg excretion significantly correlated with urogenital tract morbidity in the young but not in adults -> prevalence of urinary schistosomiasis decreases with age but FGS prevalence remain stable (chronic condition) (Poggensee 1996, 1998, Poggensee 2000, Kjetland 2005 & 2008)

Discussion

Scarcity of study on FGS and HIV
Biological, histological, clinical and epidemiolgical arguments for FGS being a risk factor for HIV infection
No easy to use, point of care, sensitive and specific FGS diagnostic tool makes FGS difficult to identify.
Gynecology aspect of women health neglected?
No prospective randomized intervantional trial to investigate the impact of FGS treatment on HIV incidence because of ethical issues (Stillwaggon 2012)

What are the biases?



Bias du to observational studies/cross sectional studies

FGS favorized by HIV infection (cf. cervical dysplasy)? A comparative study of FGS among HIV positive and negative women have shown no difference (Kleppa 2015)

Eggs exctretion increased in HIV+ -> increase the association? Several studies have shown that eggs excretion is similar or even decreased in HIV-infected patients

HIV infection could occur before FGS? Age prevalence curves predict that it is more likely to be infected with schistosomes before to encounter HIV-1

What are the confounders in the HIV and FGS association? What could be associated with both HIV and FGS? Socio-economic factors ? Biological facotrs? We need further observational studies adjusted for confounders?

Other biases: FGS diagnostic bias – what is the gold standard?
Literature review publication biases

Other possible effect of Schisto on HIV transmission

Several studies have shown that schistosomiasis increases HIV viral load in co-infected patients. In one the model shows that for each episode of schistosomiasis infection, there are 8.5 (2.7th– 97.5th percentile: 0.2–38.6) excess onward HIV-1 transmission (Baggaley 2015)

S. haematobium infection increases virus shedding into the semen of HIV-infected men as a result of egg-induced inflammation in the seminal vesicles and prostate (Leutscher 2005)

S. Mansoni associated with HIV in some epidemiological studies and primate models

TH1->Th2 immunological response favorized by

Cost effectectiveness of schistosomiasis treatment considering its potentiel effect on HIV/AIDS prevention

120,000 new cases of HIV/AIDS could be prevented through regular praziquantel treatments in the next decade. It would cost approximately $112 million. (PEPFAR $18.8 billion over 5 years).(Hotez 2009)

Annual PZQ MDA to school-age children during 10 years to prevent HIV transmission due to FGS could result in net **savings of US$16 –101 million** in Zimbabwe. It would reduce FGS aquisition as well and could therefore result in net savings of another US$ 36 - 92 million over a decade.(Ndeffo Mbah 2013)

Conclusion

What if female genital schistosomiasis is a risk factor for HIV infection?

Other observational studies looking for FGS and HIV with potential confounders adjustment are required.

How much proof do we need to intervene on schisto and on FGS prevention knowing that the causal relationship between FGS and HIV will be extremely difficult to proove experimentally.

Some evidence exists and relatively cheap intervention could eventually prevent HIV infection **and for sure** impact the important schistosomiasis burden of disease

What do public health autorithies wait to include schistosomiasis prevention in their top priorities?

Thank you!

Herman Feldmeier
Professor of Tropical Medicine
Institute of Microbiology and Hygiene Charité
University Medicine, Germany

Eyrun Floerecke Kjetland
MD, PhD, Research Fellow, Clinician
Norwegian Centre for Imported and Tropical Diseases

Jutta Reinhard-Rupp
Head of Translational Innovation Platform Global
Health, R&D
Merck Serono S.A.