How low can you go: the impact of a modestly effective HIV vaccine compared with male circumcision

John M. Kaldor and David P. Wilson

Objective: The first evidence of modest effectiveness of an HIV vaccine was demonstrated by the RV144 trial in Thailand in 2009. Although promising, this vaccine has largely been dismissed because it only had 30% efficacy. In contrast, male circumcision is widely supported and has approximately twice the efficacy, but can only be targeted to half of the population. We question the vaccine efficacy required before being considered in prevention strategies.

Design: We forecast the expected population-level impact of implementing circumcision among males compared with a 30% effective vaccine among males and females.

Methods: A mathematical transmission model was developed to describe the HIV epidemics in two different settings, Thailand and South Africa, and to forecast the expected impact of circumcision or vaccine interventions.

Results: Interventions using a vaccine with 30% efficacy would likely have a greater population benefit than male circumcision because a proportion of males are already circumcised, thus diminishing the potential target population. Both males and females will receive considerable benefit from vaccination (for example, 33% of infections averted for males and 36% for females in South Africa), whereas females will receive only moderate benefit from male circumcision (for example, 47% of infections averted for males and 19% for females in South Africa). In both settings, it would likely take a number of years before the interventions could have a noticeable impact on HIV epidemics.

Conclusion: A moderately effective vaccine, such as the one demonstrated in the RV144 trial, may have a potential role in public health programs.

AIDS 2010, **24**:2573–2578

Keywords: HIV, male circumcision, mathematical model, South Africa, Thailand, vaccine

Introduction

In 2009, a consortium of Thai and United States researchers published a report stating that for the first time a vaccine had successfully protected humans against infection with HIV [1]. Coming after a series of setbacks in HIV vaccine development, this result was hailed around the world as an important milestone in the

National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, Australia.
Correspondence to Dr David P. Wilson, National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, Australia CFI Building, Corner Boundary and West Streets, Darlinghurst, Sydney NSW 2010, Australia.
Tel: +61 2 9385 0900; fax: +61 2 9385 0920; e-mail: dp.wilson@unsw.edu.au
Received: 4 May 2010; revised: 21 July 2010; accepted: 25 July 2010.

DOI:10.1097/QAD.0b013e32833ead96

long-term fight against the global HIV pandemic, but commentators were also cautious about the implications of the finding [2–4]. Questions were raised about the choice of statistical methodology, and whether the difference between randomized groups really was significant at the 5% level, but the main concern was the modest size of the reduction in HIV incidence. No matter which way the data were analyzed the best-case scenario was relative protection of approximately 30%. Critics of the RV144 trial asserted that even if the result was real and that HIV incidence was reduced in the vaccinated group, a reduction in risk of this magnitude was far too small for the vaccine to be of any public health benefit.

Is 30% efficacy truly too low to warrant programmatic use of a vaccine? The question of how much protection a prevention agent should offer before it can be recommended for wide use in public health programs cannot be answered in absolute terms. The vaccines recommended by the WHO [5] are recognized as offering long-term protection at very high levels of efficacy. On the other hand, vaccines with lower levels of protection, such as those against typhoid [6], cholera [7,8] and tuberculosis [9,10] have been proposed for use in particular populations or circumstances. In the field of HIV prevention, there have been many trials of new agents and medical strategies to prevent infection, but so far only one approach, male circumcision, has been unequivocally demonstrated to be effective (although there is now renewed optimism over the potential for prevention through vaginal microbicides, following the release of the results of the CAPRISA 004 trial [11]). Three large-scale randomized trials of circumcision in Africa were remarkably consistent in finding that this surgical intervention reduced men's risk of acquiring HIV infection by 60%. As a consequence of these trials and other research showing that circumcision was acceptable to men and their female partners, as well as being cost-effective under standard criteria for evaluating health interventions, male circumcision has been recommended by the WHO, and is currently the subject of implementation programs in several African countries. Development of this recommendation was by no means uncontroversial, with major debates unfolding around the potential for circumcision to undermine other forms of prevention such as condom promotion, and concerns about the ability of the health system to deliver circumcision on a large scale. Nevertheless, several African countries are now rapidly expanding male circumcision programs, but high coverage is likely to be achieved only after a number of years.

While male circumcision has an indisputable benefit for HIV prevention, it has a fundamental limitation, in that it only applies to half the population, with the benefits to adolescent girls and women evident at a secondary level, as male infection rates are reduced. Therefore, in a simplistic sense, male circumcision at a whole population level is an intervention that has a 30% benefit, rather than the usually cited 60%. Coincidentally, this is exactly the same level of protection that may be provided by the vaccine investigated in the recent Thai trial, provided the results are not owing to a statistical fluke, or type I error. A vaccine would clearly have some major programmatic advantages over circumcision in that it can be administered in minutes by a wide variety of clinical personnel, does not require any specific medical infrastructure, and could potentially provide direct protection for both males and females. Under these circumstances, is it reasonable to dismiss the potential public health role of the vaccine if research could unequivocally show that it had a true efficacy of 30%?

In order to explore the relative public health benefit of a 30% effective vaccine and male circumcision in more detail, we developed a mathematical model for HIV transmission and used it to quantitatively compare the impact of the two interventions, under various implementation scenarios in the context of the Thai and South African HIV epidemics.

Methods

We developed a mathematical transmission model that tracked changes over time in the numbers of people in a population without HIV infection, with HIV infection but untreated, or receiving antiretroviral therapy for HIV infection. The model shared key features with those that have been used by our group and others [12–14]. It stratified the population of sexually active adults by sex (male/female), age (16–49 years, in 1 year age groups) and susceptibility status (uncircumcised or circumcised and vaccinated or unvaccinated), and made use of difference equations to transition the number of people in each population stratification and HIV-related health state each year over the 20-year period 2010–2029. The model difference equations of the number of people, of age i, in each health stage over time are:

$$S_{M,i,0}(t+1) = (1-\mu_S-\lambda_{M,i,0})S_{M,i-1,0}(t)$$
for unvaccinated and uncircumcised males;

$$S_{M,i,1}(t+1) = (1-\mu_S-\lambda_{M,i,1})S_{M,i-1,1}(t)$$
for unvaccinated, circumcised males;

$$S_{M,i,2}(t+1) = (1-\mu_S-\lambda_{M,i,2})S_{M,i-1,2}(t)$$
for vaccinated, uncircumcised males;

$$S_{M,i,3}(t+1) = (1-\mu_S-\lambda_{M,i,3})S_{M,i-1,3}(t)$$
for vaccinated and circumcised males;

$$I_{M,i}(t+1) = (1-\mu_I-1/\tau)I_{M,i-1}(t) + \sum_{j=0}^{3}\lambda_{M,i,j}S_{M,i-1,j}(t) \quad \text{for HIV-infected males;}$$

$$T_{M,i}(t+1) = (1-\mu_T)T_{M,i-1}(t) + {}^{1}/_{\tau}I_{M,i-1}(t)$$
for HIV-infected males receiving treatment;

$$S_{F,i,0}(t+1) = (1-\mu_S-\lambda_{F,i,0})S_{F,i-1,0}(t)$$
for unvaccinated females;

$$S_{F,i,1}(t+1) = (1-\mu_S-\lambda_{F,i,1})S_{F,i-1,1}(t)$$
for vaccinated females;

$$I_{F,i}(t+1) = (1-\mu_I-1/\tau)I_{F,i-1}(t) + \sum_{j=0}^{1}\lambda_{F,i,j}S_{F,i-1,j}(t) \quad \text{for HIV-infected females;}$$

$$T_{F,i}(t+1) = (1-\mu_T)T_{F,i-1}(t) + 1/\tau\, I_{F,i-1}(t)$$
for HIV-infected females receiving treatment.

Here, the μ parameters refer to health-state-specific mortality rates, τ is the average time from HIV-infection until commencement of antiretroviral treatment, and the λ parameters refer to the 'force of infection' or per-capita annual risk of acquiring HIV. The force of infection in this model depends on the prevalence of HIV among people in the pool of potential sexual partners. We assumed assortative sexual mixing, such that females may have male sexual partners between the ages of 1 year younger and 3 years older than themselves. The risk of infection changed over time as HIV prevalence evolved dynamically in the presence of the intervention. The force of infection for susceptible males (λ_M) and females (λ_F) was modeled according to the following mathematical expressions:

$$\lambda_{M,i,k} = \frac{\sum_{j=i-3}^{i+1}(I_{F,j}+\varphi T_{F,j})}{\sum_{j=i-3}^{i+1}(S_{F,j}+I_{F,j}+\varphi T_{F,j})}\beta_M(1-\varepsilon_v\delta_{v,k})(1-\varepsilon_c\delta_{c,k})$$

$$\lambda_{F,i,k} = \frac{\sum_{j=i-1}^{i+3}(I_{M,j}+\varphi T_{M,j})}{\sum_{j=i-1}^{i+3}(S_{M,j}+I_{M,j}+\varphi T_{M,j})}\beta_F(1-\varepsilon_v\delta_{v,k}),$$

where i denotes age, k denotes circumcision or vaccination status, S, I, and T represent the total number of susceptible people (including combinations of vaccination or circumcision status), untreated HIV-infected people, and treated HIV-infected people respectively with $\delta_{v/c,k} = 1$ if the associated group is vaccinated/circumcised and else $\delta_{v/c,k} = 0$. The parameters ε_v, ε_c, β_M and β_F represent the protective effectiveness of vaccination, circumcision and the annual risk of HIV-transmission to males and females in discordant sexual partnerships, respectively. The latter two parameters represent an average probability of HIV-transmission per discordant partnership, implicitly incorporating condom usage and frequency and type of sexual act. In this model, we assume that sexual behavior does not change over time. We assume that treated people have $\varphi = 92\%$ reduced infectiousness [9–13]. Circumcision reduced the rate of HIV acquisition by 60% for males [15–17] and the vaccine reduced it by 30% for both males and females [2,3]. Parameters used in the model are presented in Table 1. The model was implemented in MS-Excel.

The model was separately calibrated for two separate settings, Thailand and South Africa, in which all transmission was assumed to be heterosexual. The model incorporated age-specific HIV prevalence levels, average annual incidence, and circumcision rates [18–24]. The Thai model was initialized with male circumcision rates of 13% and overall population HIV incidence of 0.16% for males and 0.12% for females [18–22]. The South African model was initialized with a male circumcision rate of 35% and HIV incidence of 1% for males and 1.5% for females [18,21,23,24]. Simulated implementation of vaccine or circumcision interventions commenced in 2010 and was offered at age 16, assumed to be the debut of sexual activity in both males and females.

We considered scenarios under which circumcision was undertaken by 75 or 100% of eligible males just prior to sexual debut (assumed to be at 16 years of age), or vaccination was received by 75 or 100% of males and females just prior to sexual debut. We did not simulate interventions targeting older age groups. For each scenario, we used the model to estimate how many infections would be expected to occur each year with and without the intervention.

Results

According to our model, a vaccine with 30% efficacy would have a greater benefit than male circumcision in both the Thailand and South Africa scenarios (see Fig. 1). Administration of the vaccine among all 16 year olds in the Thailand setting would avert 44% of infections over the next 20 years among the cohort of people, who attain age 16 during this time interval and are, therefore, targeted by the interventions. In the South African setting, 35% of infections would be averted. In comparison, circumcision would avert 39% of infections in Thailand and 31% in the South African setting. The population-level advantage of the vaccine over circumcision arises primarily because a proportion of males is already circumcised, so the potential target population for a circumcision intervention is less than the potential coverage of a vaccine intervention.

In both Thailand and South Africa, it would take a number of years before the interventions could have a noticeable impact on HIV epidemics at a population level because of the time required for people to age, such that sufficient population coverage is reached. However, in those directly targeted for the intervention, there would be a marked reduction in incidence within a few years (Fig. 2). In both countries, administration of a 30%

Table 1. Parameter values used in the mathematical model.

Parameter		Thailand		Africa	
Background male circumcision prevalence		13.3%		35%	
Initial population-level HIV incidence		Male 0.16%	Female 0.12%	Male 1%	Female 1.5%
Initial HIV prevalence	Age group (years)	Male (%)	Female (%)	Male (%)	Female (%)
	15–19	0.01	0.02	2.50	6.70
	20–24	0.11	0.14	5.10	21.10
	25–29	0.39	0.31	15.70	32.70
	30–34	0.46	0.30	25.80	29.10
	35–39	0.34	0.20	18.50	24.80
	40–44	0.19	0.12	19.20	16.30
	45–49	0.10	0.06	6.40	14.10
		Male	Female	Male	Female
Annual transmission risk in 2009 over discordant partnerships over all partners and risk exposures per year (β_M/β_F: calibrated to match overall population incidence rate in each setting)		0.395	0.234	0.06	0.144
Annual probability of death for uninfected people				0.002	
Annual probability of death for untreated HIV-infected people				0.015	
Annual probability of death for HIV-infected people on ART				0.01	
Average number of years from HIV infection to initiating ART				8 years	

ART, antiretroviral therapy.

effective vaccine would continue to be more advantageous than circumcision over time (Fig. 2). Additionally, both sexes will receive considerable benefit from vaccination (for example, 33% of infections averted for males and 36% for females in South Africa), whereas females will receive only moderate benefit from male circumcision (for example, 47% of infections averted for males and 19% for females in South Africa).

Discussion

Through a mathematical model, we have shown that a preventive vaccine with efficacy of 30% will have a greater effect on reducing HIV transmission and prevalence than male circumcision. For Thailand, where HIV prevalence and circumcision rates are lower, the relative effect of male circumcision compared with the vaccine would be greater than in South Africa.

In addition to infections averted, the cost, acceptability and risk of the two interventions would also have to be taken into account in a comprehensive comparative analysis. The costs associated with male circumcision have been estimated at approximately US$50–70 per operation [25,26]. This cost does not include the training of additional healthcare workers or providing additional clinical facilities, both of which will be needed to carry

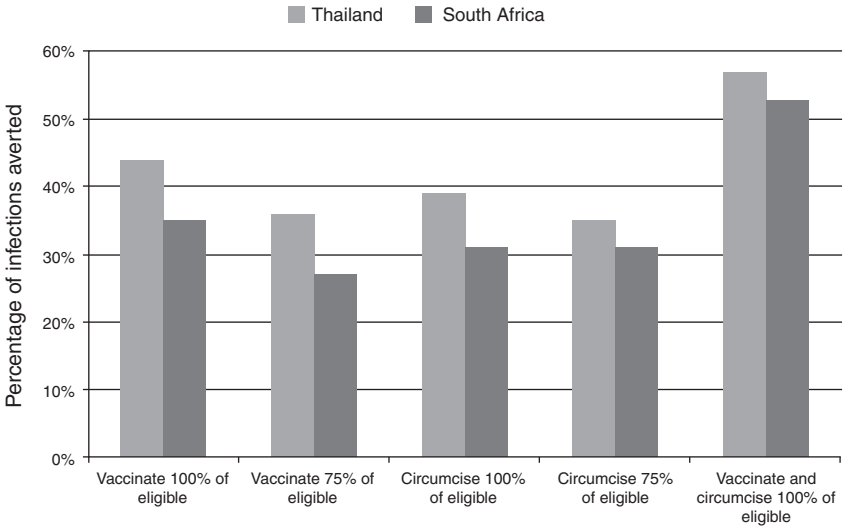

Fig. 1. Estimated percentage of HIV infections averted over 20 years among people of the age group in which interventions were targeted, for vaccination, male circumcision and both. Interventions are targeted at people just prior to entry to the sexually active population. Over time, the cumulative cohort of targeted populations increases in size.

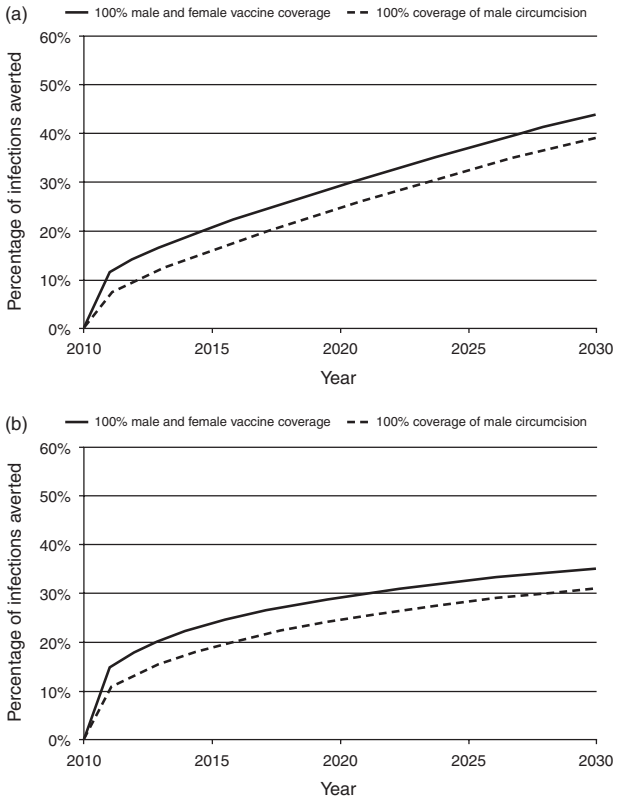

Fig. 2. Projections of the impact of circumcision versus vaccination interventions on the percentage of HIV infections averted among people of the age group in which interventions were targeted in (a) Thailand and (b) South Africa. That is, over time as more people enter the sexually active population, the targeted population for interventions increases in size. The percentage of infections averted in this increasing cohort over time is presented.

out a large-scale expansion of male circumcision. Costing of a vaccine is entirely hypothetical at this stage. By analogy with hepatitis B virus, human papillomavirus and other vaccines, initial prices would be in the several hundred dollar range, but there could be a rapid drop in price with volume and through negotiation with public and foundation sponsors. In a population with very low current levels of circumcision, the number of interventions would be twice as high for vaccination as it would be for circumcision to achieve approximately the same relative reduction in incidence. Therefore on this theoretical basis, cost-effectiveness would be roughly equal once the price of vaccination fell to roughly half that of the circumcision operation. The relative uptake of the two interventions is also difficult to quantify at present, but it is likely that a vaccine would prove to be more widely accepted. The short-term medical risks of male circumcision are well quantified in a trial setting, but may be greater as the procedure is offered more widely through routine programs. The corresponding risks for an HIV vaccine are as yet unknown. It is also important to note that both interventions may lead to an increase in unsafe sexual behavior, if recipients believe that they are fully or substantially protected. Another important difference between the two interventions is that circumcision is understood to confer permanent protection, whereas the protection that may be conferred by a vaccine could wane over time, as suggested by the results from the Thai trial [1].

In reality, the greatest question is whether the RV144 vaccine actually works, regardless of its level of efficacy. An answer to this question can only come from further clinical research that will be very expensive and take a number of years to complete. However, an effective vaccine is recognized as the ultimate solution to global HIV control, and with no other construct currently showing the promise of substantial protective efficacy such an investment should not be dismissed without due consideration and debate. The purpose of our analysis was to inform this debate and specifically to model the impact of a low-efficacy vaccine, compared with the widely accepted intervention of male circumcision. It is essential that the scientific and public health community remains open to the potential benefit of any strategy that can help to alleviate the burden of the ongoing HIV pandemic [27].

Acknowledgements

J.M.K. is supported by a Research Fellowship from the National Health and Medical Research Council and D.P.W. is supported by a Research Fellowship from the Australian Research Council. The National Centre in HIV Epidemiology and Clinical Research is funded by the Australian Government, Department of Health and Ageing. The views expressed in this publication do not necessarily represent the position of the Australian Government. NCHECR is affiliated with the Faculty of Medicine. The authors thank Bridget Haire for stimulating discussions that gave rise to key ideas in the paper.

References

1. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, *et al.* **Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand.** *N Engl J Med* 2009; **361**:2209–2220.
2. **A (prime) boost for HIV vaccine research?** *Lancet* 2009; **374**:1119.
3. Cohen J. **HIV/AIDS research: surprising AIDS vaccine success praised and pondered.** *Science* 2009; **326**:26–27.
4. **HIV vaccine trials and tribulations**. *Lancet Infect Dis* 2009; **9**:651.
5. *Immunization, vaccines and biologicals*. http://www.who.int/immunization/topics/en/index.html. Geneva: World Health Organization; 2009.

6. Fraser A, Goldberg E, Acosta CJ, Paul M, Leibovici L. **Vaccines for preventing typhoid fever**. *Cochrane Database Syst Rev* 2007; (**3**):CD001261.
7. Graves PM, Deeks JJ, Demicheli V, Jefferson T. **Vaccines for preventing cholera: killed whole cell or other subunit vaccines (injected)**. *Cochrane Database Syst Rev* 2001; (**1**): CD000974.
8. **Cholera vaccines: WHO positional paper**. *World Health Organization Wkly Epidemiol Rec* 2001; **76**:117–124.
9. Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, *et al*. **Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature.** *JAMA* 1994; **271**:698–702.
10. **BCG vaccine: WHO position paper**. *Wkly Epidemiol Rec* 2004; **79**:25–40.
11. Karim QA, Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, *et al*. **Effectiveness and safety of tenofovir gel: an antiretroviral microbicide for the prevention of HIV infection in women.** *Science* 2010 [Epub ahead of print].
12. Anderson JS, Wilson DP, Templeton DJ, Grulich AE, Carter R, Kaldor JM. **Cost-effectiveness of adult circumcision for HIV prevention in men who have sex with men in a resource-rich setting.** *J Infect Dis* 2009; **200**:1803–1812.
13. McLean AR, Blower SM. **Imperfect vaccines and herd immunity to HIV.** *Proc Biol Sci* 1993; **253**:9–13.
14. Anderson R, Hanson M. **Potential public health impact of imperfect HIV type 1 vaccines.** *J Infect Dis* 2005; **191 (Suppl 1)**:S85–S96.
15. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. **Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial.** *PLoS Medicine* 2005; **2**:1112–1122.
16. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, *et al*. **Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial.** *Lancet* 2007; **369**:643–656.
17. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, *et al*. **Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial.** *Lancet* 2007; **369**: 657–666.
18. *Information package on mail circumcision and HIV prevention: the global prevalence of male circumcision*. Geneva: World Health Organization; 2007. pp. 2.
19. Castellsague X, Peeling RW, Franceschi S, de Sanjose S, Smith JS, Albero G, *et al*. **Chlamydia trachomatis infection in female partners of circumcised and uncircumcised adult men.** *Am J Epidemiol* 2005; **162**:907–916.
20. *HIV infections by age and sex, Thailand*. Bangkok, Thailand: Bureau of Epidemiology, Department of Disease Control, Ministry of Health Thailand; 2009.
21. UNAIDS 2008 Report on the global AIDS epidemic. www.unaids.org
22. WHO. *Global tuberculosis control, WHO report 2008, country profile: Thailand*. Geneva: World Health Organization; 2008. pp. 149–152.
23. Connolly C, Simbayi LC, Shanmugam R, Nqeketo A. **Male circumcision and its relationship to HIV infection in South Africa: results of a national survey in 2002.** *S. Afr Med J* 2008; **98**:789–794.
24. Rehle T, Shisana O, Pillay V, Zuma K, Puren A, Parker W. **National HIV incidence measures: new insights into the South African epidemic.** *S Afr Med J* 2007; **97**:194–199.
25. Kahn JG, Marseille E, Auvert B. **Cost-effectiveness of male circumcision for HIV prevention in a South African setting.** *PLoS Med* 2006; **3**:e517.
26. White RG, Glynn JR, Orroth KK, Freeman EE, Bakker R, Weiss HA, *et al*. **Male circumcision for HIV prevention in sub-Saharan Africa: who, what and when?** *AIDS* 2008; **22**:1841–1850.
27. Attia S, Egger M, Muller M, Zwahlen M, Low N. **Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis.** *AIDS* 2009; **23**:1397–1404.