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HIV PREVENTION RESEARCH: TAKING STOCK AND THE WAY FORWARD

Richard Hayes, Saidi Kapiga, Nancy Padian, Sheena McCormack, and Judith Wasserheit

Abstract

Previous papers in this supplement have reviewed the evidence of the effectiveness of alternative HIV prevention methods from randomised controlled trials and other studies. This paper draws together the main conclusions from these reviews. A conceptual framework is presented that maps the proximal and distal determinants of sexual HIV transmission and helps to identify the stages in the causal pathway at which each intervention approach acts. The advances, gaps and challenges emerging from the reviews of individual intervention methods are summarised and cross-cutting themes identified. Approximately 90% of HIV prevention trials have found no effect on HIV incidence and we explore the alternative explanations for the large number of “flat” trials. We conclude that there is no single explanation for these flat results which may be due to interventions that are ineffective or inappropriately targeted or implemented, or to factors related to the design or conduct of trials. We examine the lessons from these flat results and provide recommendations on what should be done differently in future trials. HIV prevention remains of critical importance in an era of expanded delivery of antiretroviral therapy. In future HIV prevention research, it is important that resources are used as efficiently as possible to provide rigorous evidence of the effectiveness of a wider array of complementary prevention tools.

Keywords

HIV; prevention and control; randomized controlled trials; sub-Saharan Africa

INTRODUCTION

Previous papers in this supplement have reviewed current evidence on the efficacy of alternative behavioural and biomedical approaches to HIV prevention, based on data from intervention trials and other studies and with a primary focus on prevention of sexually transmitted HIV infection in sub-Saharan Africa [1-7]. In this final paper, we summarise the key findings emerging from these reviews and discuss the way forward.

We begin by mapping the proximal and distal determinants of sexual HIV transmission, identifying how the alternative approaches to HIV prevention target different points on the causal pathway. We then summarise the advances, gaps and challenges emerging from our review of each of the main intervention approaches, and identify a number of cross-cutting themes.

It is striking that almost 90% of the trials carried out to measure the impact of these interventions have shown no effect on HIV incidence. We go on to explore the potential reasons for the large number of “flat” trials in this area of research. An important conclusion is that there is no single or simple explanation for these flat trials. In some cases, flat results reflect interventions that are ineffective or inappropriately targeted or implemented. In other

cases, factors in trial design or conduct may conspire to produce flat results, even for interventions that are potentially effective.

Based on these observations, we consider the important question of what the HIV prevention research community should do differently in the future, if we are to improve the efficiency and cost-effectiveness of our efforts to identify interventions that will be effective in controlling the HIV epidemic in sub-Saharan Africa.

A CONCEPTUAL FRAMEWORK

Sexual transmission of HIV infection is influenced by a complex combination of biomedical, behavioural and socio-cultural factors. A simplified conceptual framework may be helpful in identifying potential targets for which synergistic sets of interventions could be assembled. One such conceptual framework is presented in Figure 1.

Determinants of sexual HIV transmission operate on at least three, reciprocally interacting levels that range from the microbiological and cellular levels through the individual and local community levels, to the population and global levels. At the ***microbiological and cellular levels***, transmission depends on exposure of susceptible hosts to the pathogen (HIV), and can be modulated by factors that alter host susceptibility and viral infectiousness, including a range of frequently recurrent or persistent co-infections. The risk of transmission is directly related to the viral load in HIV-infected individuals, and may vary according to viral subtype [8,9]. For any given level of plasma viral load, transmission risk may be modified by the host's local or systemic immune response. Important co-infections that may increase viral load in the genital compartment or the susceptibility of the host include sexually transmitted infections (STIs), and other genital infections such as bacterial vaginosis (BV). Non-genital infections such as malaria, tuberculosis or helminths may also increase HIV viral load in the infected partner [10].

At the ***individual and community levels***, the biomedical variables governing exposure to the virus and the risk of transmission are strongly influenced by individuals' behaviours (and those of their partners), local sexual networks and community health care systems. Sexual behaviours and networks determine the frequency and type of sexual contact between infected and uninfected partners. Health-seeking behaviours and health systems determine the likelihood that individuals access effective services providing HIV testing, prevention and care, as well as treatment for co-infections, including other STIs. These factors may thus influence biomedical variables such as HIV viral load and resistance patterns or co-infection prevalence. Intra-vaginal cleansing and other practices may also affect HIV transmission risk by altering host defences against HIV and/or co-infections [11].

Finally, at the ***population and global levels***, behavioural and biomedical variables are, in turn, shaped by a wide range of underlying determinants, including socio-cultural, economic, political, technological, epidemiological and demographic factors. These distal determinants combine in complex ways to influence the behaviours and biomedical parameters that govern the probability of HIV transmission, and may in turn be affected by these parameters.

This conceptual framework helps identify important links in the causal chain of HIV sexual transmission. Each link provides a potential target for preventive interventions (Table 1). Interventions that target determinants at the microbiological and cellular levels, if effective and feasible, are likely to have more rapid and consistent effects that are easier to demonstrate in randomized controlled trials (RCTs) than interventions that operate at more distal points. This is because their impact is more direct, rather than functioning through multiple mediating factors.

Because the causal pathway may vary somewhat in different populations, interventions targeted at distal determinants may be more effective in some settings than others, with important consequences for the generalisability of trial results. The scale of such interventions may also pose difficulties for the conduct of RCTs, and the long causal pathway may mean that effects on HIV transmission may take many years to be seen. Biomedical interventions, if they are intrinsically effective, may be less susceptible to these problems of evaluation. However, problems of generalisability may still affect some of these interventions, particularly those that require high adherence (which is likely to differ in different settings) or those that target co-infections (the prevalence of which may vary between populations) as we have seen for STI treatment as an HIV prevention strategy [2].

This conceptual framework also highlights the potential value of evaluating combinations of partially effective interventions that may work synergistically at multiple points in the causal pathway. In the near to medium-term, it is likely that optimal HIV prevention strategies will be those that offer packages of interventions within and across the three levels in a topology that is tailored to sub-populations defined, at a minimum, by gender, HIV status and ART eligibility [7]. Evaluation of combination prevention packages also presents opportunities for development of new methodological approaches that will advance prevention research more broadly.

ADVANCES, GAPS AND CHALLENGES

Individual papers in this series have discussed the main approaches to prevention in detail. Here we briefly summarise the key findings of these papers and draw out some cross-cutting themes.

Behavioural interventions

While it is clear that patterns of sexual behaviour are important determinants of HIV transmission, and documented changes in behaviour have played a role in reductions in HIV incidence in a range of countries, it is less clear what specific interventions are able to bring about such changes. Of nine RCTs reviewed by Ross [1], evaluating five major approaches to behavioural intervention, none has shown a significant effect on HIV incidence, although some trials have shown important effects on knowledge, attitudes, reported behaviour and STIs. A number of explanations are advanced for these disappointing results, including limitations in the delivery or intensity of interventions, limited follow-up time, the overriding influence of cultural norms and socio-economic factors, inadequate power and a high intensity of intervention in control arms. The trial results emphasise the importance of biomedical endpoints in RCTs of behavioural interventions, because of the unreliability and bias associated with self-reported sexual behaviour. Detailed process evaluation and qualitative research are also critical to help interpret positive or negative results.

Areas for future research include interventions targeting HIV-infected individuals (positive prevention); further work on effective counselling strategies for HIV-negative individuals accessing voluntary counselling and testing (VCT) services; interventions designed to reduce concurrent sexual partnerships; interventions among youth that address social norms and wider community influences; and approaches to help maintain risk reduction behaviours.

STI treatment for HIV prevention

There is compelling evidence from observational, clinical and biological studies that HIV acquisition and transmission are enhanced in the presence of other STIs, but only one of nine trials has shown a significant impact of an STI treatment intervention on HIV incidence [2]. For interventions targeting curable STIs, explanations for these findings include the

influence of HIV epidemic stage (with less effect of curable STIs in mature epidemics), population prevalence of STIs, intensity of interventions in control arms and inadequate power. For herpes suppressive therapy, it appears that current treatment regimens are insufficiently potent to avert the cellular and inflammatory effects of genital herpes, and that the reduction in HIV plasma viral load in HIV-positive individuals is insufficient to produce a measurable effect on HIV transmission.

Areas for future work include the development of more potent interventions against herpes simplex virus type 2 (HSV-2), including prophylactic vaccines; interventions to control highly prevalent vaginal conditions including bacterial vaginosis or to modify intra-vaginal practices; methods for the diagnosis and treatment of STIs that are an improvement on current syndromic approaches; and research on the interaction of human papillomavirus (HPV) and HIV, including trials of the impact of HPV vaccines on HIV incidence.

Antiretroviral treatment for HIV prevention

The roll-out of antiretroviral treatment (ART) in low and middle income countries has been successful in reducing mortality and improving the quality of life among people living with HIV/AIDS. Existing evidence shows that ART is effective in protecting uninfected individuals following exposure to HIV infection (post-exposure prophylaxis or PEP). Current guidelines recommend use of a full 28-day triple ART regimen for occupational exposure as well as non-occupational exposure if there is a substantial risk of HIV transmission from a known HIV-infected person or a person whose HIV status is unknown. In addition, ART may be used to protect individuals known to be HIV uninfected prior to exposure to the virus (pre-exposure prophylaxis or PrEP). Results from animal studies and the success of ART in preventing mother-to-child transmission of HIV strongly suggest that PrEP could be effective in preventing HIV acquisition. Currently, 11 phase II and III RCTs of PrEP using different drugs and regimens are ongoing and results will be available during the next few years [3].

Universal voluntary HIV testing followed by immediate treatment of all infected individuals, irrespective of their CD4 counts, has been proposed as a new strategy for HIV prevention. This Universal Test and Treat (UTT) strategy aims to reduce infectiousness at a population level, thereby reducing HIV incidence. Implementation of UTT is clearly challenging given that a substantial proportion of those individuals who are currently HIV-infected and eligible for treatment do not receive it. Some mathematical models [12] have shown that such an approach could potentially result in elimination of HIV epidemics as well as reducing morbidity and mortality in HIV-infected individuals, although others have pointed to the limitations of these models [13]. Plans for feasibility studies and cluster randomised trials (CRTs) to evaluate this strategy are currently under preparation.

Topical microbicides

Topical microbicides represent a potential HIV prevention tool that could be controlled by women [4]. Two generations of microbicides have gone through large scale efficacy trials among women at high risk of HIV infection in Africa. The products tested include nonoxynol-9, SAVVY, cellulose sulphate, Carraguard, PRO 2000 and BufferGel. Disappointingly, none of these products has been shown to be effective. A number of challenges have been encountered during the conduct of these trials, including difficulties in measuring adherence to product use, high pregnancy rates among trial participants, potential safety concerns and lack of adequate animal models that reliably predict effects in humans. The trials, however, have shown that the concept of a vaginally inserted HIV prevention gel is highly acceptable and, if available, would be used by women.

The field is now moving forward to test new microbicides based on antiretroviral therapeutic compounds, supported by data from both in vitro studies and animal models. The most advanced candidate is tenofovir, with dapivirine and UC781 close behind and several others planned for Phase I trials. Although these products are expected to be highly specific for HIV, there are concerns that intravaginal use may lead to systemic absorption and toxicity, and potential development of viral resistance to ARVs. Although research to date suggests that the risk of these complications is low, further research will be required among women enrolled in large-scale efficacy trials and from Phase IV post-marketing studies.¹

Vaccines

The development of an effective HIV vaccine has proved very challenging and while there have been nearly 200 Phase I and II trials of vaccine candidates, only five Phase IIb and III efficacy trials have been conducted, of which only one has shown evidence of modest protection [5]. Trial findings have emphasised the limitations of animal models, with products predicted to be effective showing no benefit in human trials and vice versa.

Building on the recent trial in Thailand showing that a prime-boost vaccine resulted in 31% reduction in HIV incidence (although of marginal statistical significance), future work will explore more effective prime-boost regimens that attempt to provoke broadly neutralising antibodies (against a wide variety of viral types), as well as effective cell-mediated immunity. An important immediate priority is to gain insights about correlates of protection from the Thai trial. Future vaccine trials will face difficult questions regarding choice of study population, sample size requirements and what standard of prevention and care should be provided to the control arm.

Male circumcision

The efficacy of male circumcision (MC) in preventing female-to-male transmission has been definitively established in three RCTs in South Africa, Kenya and Uganda. The effects on male-to-female transmission are less clear, with some evidence of a protective effect from observational studies but no useful RCT evidence because the only trial was terminated early as numbers were insufficient to provide adequate power [6]. Similarly, the observational evidence of protection among men who have sex with men (MSM), including those who primarily engage in insertive anal intercourse, is unclear and there have been no RCTs. The extent to which the protective effect against female-to-male transmission is mediated by effects on ulcerative STIs also remains unclear.

Although there may be a place for an RCT among MSM, future work is likely to focus on operational research on the delivery of safe and cost-effective services for MC in resource-poor settings. Research is needed to measure any increases in risky sexual behaviour following expansion of MC services, and to develop and evaluate counselling interventions among young men presenting for circumcision. Expanded education about and access to safe neonatal circumcision is another important area of work.

Combination prevention

HIV prevention efforts have focused on a range of strategies, including behaviour change programmes, STI control, MC, VCT, harm reduction, prevention of mother-to-child transmission, improved blood safety and structural interventions. There is increasing recognition that individual interventions may be insufficient and that effective population-level control of HIV transmission may require a combination of these biomedical,

¹Please see Postscript for information on results of CAPRISA004 trial of tenofovir microbicide gel which were reported in July 2010.

behavioural and structural interventions [7]. This combination prevention approach has been inspired by the recognition that countries such as Uganda, Thailand and Brazil generated sharp, sustained declines in HIV incidence using an array of known effective interventions.

Combination prevention programmes that draw upon the social sciences and community experience, as well as biomedical interventions, can identify and respond to the dynamic prevention needs of each affected population. Beyond tailoring programmes to local epidemics, it is essential that interventions be attuned to people's life conditions, address all the interacting barriers to prevention and be delivered with the intensity and quality necessary to achieve intended effects. However, it is recognized that the implementation of combination prevention requires an unprecedented level of partnership, collaboration and coordination in programme design, resourcing, management and evaluation. Importantly, although such strategies show great promise, their impact still must be demonstrated through rigorous evaluations.

CROSS-CUTTING THEMES

A number of cross-cutting themes have emerged from our review of research on alternative HIV prevention strategies. These are briefly outlined here.

Preponderance of flat trials

As recently summarised in a systematic review of late-phase RCTs of interventions to prevent sexual transmission of HIV [14], of 39 trials in which effects on HIV incidence have been measured, only five have shown a statistically significant positive effect, while one has shown a negative effect and the remaining 33 have shown no effect (Table 2). Discrepancies between numbers of trials shown in Table 2 and the individual reviews in this supplement result from differences in eligibility criteria and classification of multi-component interventions.

The five trials showing a positive effect include all three trials of male circumcision for prevention of HIV acquisition [15-17], for which the evidence of a partially protective effect is now very strong. The Mwanza trial of syndromic STI management also demonstrated a substantial reduction in HIV incidence [18], although eight other trials of a range of STI treatment strategies implemented in various settings failed to show an effect. The most recent positive result comes from the ALVAC-AIDSVAX prime-boost vaccine trial conducted in Thailand, although this result was of marginal statistical significance and showed modest efficacy [19]. The one trial showing a clear negative effect was the multicentre (COL1492) trial testing the efficacy of the vaginal microbicide nonoxynol-9 [20].

It is notable that all five positive results come from trials of biomedical interventions targeting factors at the microbiological and cellular levels that are proximal determinants of HIV transmission (centre of Figure 1). By far the strongest evidence of effectiveness is for male circumcision, a biomedical intervention that could be readily evaluated in an individually-randomised controlled trial and that does not require ongoing adherence.

The preponderance of flat results in trials of HIV prevention is clearly a matter of concern, and the possible explanations for this are outlined in a later section.

Duration of follow-up

Many of the trials of HIV prevention have had quite short periods of follow-up, typically of 1 to 2 years. While such short follow-up periods may be appropriate for some biomedical interventions, they may not be adequate for interventions targeted at behavioural or

underlying factors that are more distal determinants of HIV transmission (outer rings of Figure 1).

While structural interventions may have a substantial effect on HIV epidemics in the long-term, they are likely to take a considerable time to influence proximal determinants of HIV transmission, such as patterns of sexual behaviour, and thus to reduce HIV incidence. Behavioural interventions, while closer to HIV transmission in the causal chain, may also take time to have their full effect, especially as they may depend on changing attitudes and norms at community level. A good example is provided by behavioural interventions among adolescents, which may be undermined unless sexual norms among older adults in the community can be addressed.

Difficulties in measuring behaviours

While the focus of this review has been on trials in which HIV incidence is the primary endpoint, behavioural measurements also play an important role in many of these trials and have proved to be problematic. In trials of behavioural interventions, self-reported sexual behaviour is an important secondary endpoint, but is known to be subject to reporting bias which may be differential between study arms. It is notable that several RCTs of such interventions have found significant effects on self-reported behaviours but no effect on HIV incidence and this is likely to be due, at least partly, to reporting bias. This suggests that the many other trials which have only reported behavioural endpoints should be interpreted with great caution.

Measurement of behaviours may also be important in RCTs of biomedical interventions. For example, the frequency of anal intercourse is potentially an important issue in trials of vaginal microbicides, and accurate measures of adherence are of considerable relevance in trials of products requiring regular dosing such as microbicides, PrEP regimens and herpes suppressive therapy.

Importance of process measures

Carefully collected data on process measures (defined broadly as measures of the delivery and uptake of an intervention and of variables that are intermediate in the causal chain between intervention and primary endpoint) have proved to be of great value in trials of behavioural interventions that have shown flat results, helping investigators to explore which aspects of interventions were not delivered as intended or which did not have the effects that were intended. Such data can help in improving or reformulating such interventions. In principle, process measures can also be of value in unpacking which components of complex interventions have contributed to observed effects. In general, process measures are of most value for complex interventions and those acting at distal points in the causal chain.

Low power for HIV incidence

Many trials have had low power for HIV incidence either because they were not designed to be powered for this endpoint (as is the case for some Phase IIb trials for example), because HIV incidence was lower than expected or because of problems or delays in recruiting adequate numbers of participants. Power is sometimes low because there were no reliable data on HIV incidence in the study population before the trial commenced and sometimes because HIV incidence had fallen over time due to cohort attrition or the effects of counselling or other interventions provided within or outside the context of the trial.

Interventions provided to the control group

We have seen that many trials have provided quite intensive interventions to control group participants. In some cases, this may have significantly diluted observed effects of the intervention under study.

Limitations of animal models

The development of biomedical interventions, such as microbicides and vaccines, has been hampered by limitations in animal models. Encouraging results from animal studies have often not been borne out by the results of trials in humans.

INTERPRETATION OF FLAT TRIALS

It is clearly a matter of concern that 33 of 39 trials of interventions to prevent HIV infection, one of the world's greatest public health problems, have shown no effect. These include all trials of behavioural interventions, which remain the mainstay of HIV control programmes. In this section we briefly discuss potential explanations for these flat results.

Prevention trials may yield "flat" results that show no significant positive or adverse effect for at least three reasons, and these have different implications for policy and for future research. First, the basic concept may be flawed. Second, the underlying concept may be sound, but the specific intervention strategy may be inert or too weak to have a significant effect. Or third, issues in the design and/or conduct of the trial may preclude demonstrating an effect that, in reality, could be clinically or programmatically important.

Wrong concept

The intervention(s) evaluated in a trial may be based on an invalid concept of HIV prevention. Ideally, observational data and early phase RCTs "weed out" such interventions before resources are invested in large, late phase trials, as seems to have been the case among most HIV prevention RCTs conducted to date. While the specific classes of product evaluated in most previous trials of HIV vaccines and microbicides have been shown to be ineffective, this does not necessarily invalidate the broad concepts of vaccines or microbicides as HIV prevention tools, as evidenced by recent advances in both of these areas.

Right concept, but inadequate intervention

Sometimes an intervention approach is based on a valid concept, but the intervention itself is inadequate to prevent HIV transmission in a significant proportion of the trial population. A good example may be provided by the trials of herpes suppressive therapy for HIV prevention, which have been discussed in a previous paper in this series [2]. This approach is based on the very extensive and biologically plausible observational evidence that HIV susceptibility and infectivity are enhanced in the presence of HSV-2 infection. Despite the strong rationale for this intervention, trials of herpes suppressive therapy using twice-daily acyclovir failed to show a protective effect on HIV acquisition or transmission. It is likely that the lack of effect seen in these trials resulted from a failure of the specific treatment regimen being evaluated to completely avert the cofactor effect of HSV-2 infection on HIV transmission. There is increasing evidence that even suppressive treatment regimens, such as those used in the trials, that are highly effective in preventing or suppressing clinical episodes of genital herpes may not be potent enough to avert HIV transmission because of persistent local cellular immune responses to HSV-2 infection.

Where flat trials are explained by inadequate interventions, but there is compelling evidence that the concept is right, the appropriate response may be to develop and test more effective

interventions. The emerging data from the HSV-2 trials highlight the need to better understand the biological mechanisms underpinning the interactions between HIV and frequently recurrent or persistent co-infections such as HSV-2, malaria and tuberculosis, and to consider new regimens that will target these mechanisms. Alternatively, if treatment regimens for herpes suppression are inadequate, the search for an effective vaccine for primary prevention of HSV-2 infection becomes even more urgent.

Issues in trial design or conduct

In some trials, flat results are attributable at least partly to issues in trial design or conduct. Many of these limitations have been discussed in a previous section, but they are briefly summarised here.

Under-powered trials—Some HIV prevention trials have not been adequately powered to provide a useful estimate of impact on HIV incidence, often because incidence during the trial is lower than expected. The consequence of an under-powered trial will be that the precision of the effect estimate will be poor, so that a non-significant result cannot rule out a substantial effect.

Control group interventions—Some trials have provided participants in the control arm with interventions that were substantially enhanced compared with the local standard of care. Insofar as this results in reduced incidence in the control arm it may prevent the trial from providing valid data on the impact of the intervention, since the effect measure may be severely biased towards the null.

Adherence to intervention—Whether we are conducting an *efficacy trial*, designed to measure effect when the intervention is delivered optimally (as will usually be the case for new biomedical products such as drugs or vaccines) or an *effectiveness trial*, designed to measure the effect under practical conditions of implementation, the results of a trial and their interpretation will be strongly influenced by the level of adherence achieved. In some trials, for example those evaluating microbicides or treatment of co-infections for HIV prevention, low levels of adherence may have played a part in explaining lack of effect.

There are clearly many other potential challenges in trial conduct, for example selection bias due to losses to follow-up; measurement error; and contamination between intervention and control arms. While careful attention must be paid to all these issues, we do not think that these are the main factors explaining the flat results of the HIV prevention trials conducted to date.

Where flat trial results are due to an invalid concept or inadequate intervention, they make a valuable contribution to the field, because they provide rigorous evidence that a specific intervention approach is ineffective, and focus subsequent efforts on alternative or improved approaches. In contrast, flat trials resulting from deficiencies in trial design or conduct waste precious HIV research effort and resources, and ultimately cost lives by providing limited and confusing evidence of the effectiveness of an intervention.

WHAT SHOULD WE DO DIFFERENTLY?

After more than 20 years of HIV prevention research, it is striking that only male circumcision has been proven to be an effective preventative intervention in multiple randomised trials. While much has been learned from the growing number of flat trials, the very low proportion of trials with positive findings is disappointing. Clearly, we must consider what lessons we can learn from these trials, and whether there are things we should do differently when designing future interventions and trials

Development of interventions

The large number of flat trials in which the concept was right but the intervention was inadequate suggests that more attention should be paid to evaluating and optimising the interventions before they proceed to efficacy trials. The substantial investment needed in pre-clinical studies and early phase trials of new drugs and vaccines before these products go into large Phase III trials is well recognised, and there is a clear step-wise process based on well-established regulatory procedures, which has been expanded by the scientific community as each biomedical intervention has failed. In contrast, some behavioural and other HIV prevention interventions have been developed over a short time period and have undergone little or no preliminary evaluation before commencement of a Phase III trial.

This is due at least partly to difficulties in attracting research funding for this early intervention developmental work, and the need to move quickly once the main trial is funded. We encourage research funders and sponsors to give careful consideration to this problem and to introduce specific schemes to support the development and initial evaluation of interventions before commencement of large Phase III trials. It should be acknowledged that such projects may not result in high-profile journal publications, but may have an important pay-off in increasing the chance of positive findings in a subsequent large-scale trial.

Careful choice of study populations and epidemic phase

It is well known that study populations for Phase III trials must be carefully selected to ensure internal validity. The goals are usually to select a population that is at high risk of HIV infection and able and willing to comply with trial procedures, to ensure high adherence to the intervention, and to minimise selection bias due to losses to follow-up.

In addition, it is increasingly recognised that some interventions have differential effects in different populations or at different phases of an epidemic. We have seen, for example, that STI treatment interventions are likely to be most effective in populations with high rates of curable STIs, which are likely to play a more important role in concentrated or early-phase HIV epidemics and in communities with limited treatment services than in more generalised or mature epidemics and in populations with widespread access to high quality STI care. Yet some trials have been carried out in populations with low rates of curable STIs and with highly generalised and mature HIV epidemics. Similarly, one of the possible reasons for the limited effect seen in some trials of behavioural interventions is that they were carried out in populations in which substantial reductions in risk behaviour had already occurred as a result of prior HIV prevention activities.

When selecting study populations for trials of preventive interventions, we should carefully match the intervention to the characteristics of the population and the phase of the epidemic.

Intensity of intervention

We have already noted the distinction between *efficacy* trials, aimed at measuring intervention effects under optimal conditions, and *effectiveness* trials, aimed at measuring effects under conditions of practical implementation. It is well accepted that efficacy trials must ensure adequate intensity of intervention and high levels of adherence.

Most trials of behavioural or STI treatment interventions have been effectiveness trials, aiming to develop and evaluate interventions that would be affordable and sustainable for wide-scale implementation, for example at regional or national level. Given the lack of proven HIV preventive interventions, however, we would argue that there is an urgent need for proof of concept of new intervention approaches. With this in mind, we suggest that

future trials should aim for relatively high intensity, accepting that the intensity following routine implementation will undoubtedly be lower.

Avoiding over-intensive intervention in control arm

We have seen that a likely explanation of some of the flat trial results has been that control arm participants have received a relatively high level of intervention beyond the local standard, diluting the measured effects of the intervention and making it difficult to demonstrate impact. There has been considerable discussion of the appropriate standard of prevention and care in RCTs [21]. There is clearly a tension between the ethical requirements to avoid harm and not to withhold interventions with established efficacy from trial participants including those in the control arm, and the scientific and ethical responsibility to obtain useful evidence of the impact of an intervention that could potentially prevent millions of new HIV infections. Some have argued that it is, in fact, unethical to recruit participants to a trial that is unable to achieve its scientific objectives, particularly when it is unlikely that interventions provided to the control arm will be sustained after the end of the trial and may not be part of a standard prevention package available in the general population. This is an issue that requires further discussion and international ethical guidelines should be clarified.

Sufficient duration of follow-up

Careful attention to the appropriate duration of follow-up is also needed, and this may depend on the type of intervention. We have seen in an earlier section that some interventions aimed at more distal determinants may involve a lengthy causal pathway and may take years to exhibit their full effect. The impact of the intervention may not be seen if the duration of follow-up is too short. Similarly, the impact of population-level interventions, measured in CRTs, may increase over time because of indirect and herd effects leading to a general reduction in transmission. Conversely, the effects of some interventions may wane over time, in which case it will be necessary to measure both short-term and longer-term effects to assess durability and guide the frequency of repeat intervention to maintain prevention effectiveness.

Ensuring adequate power and precision

Several of the flat trials have not been adequately powered to detect any impact of the intervention on HIV incidence. Power calculations must be based on realistic estimates of HIV incidence during the trial. This is likely to require prior data on HIV incidence in the proposed study population. Adjustment is needed to allow for potential reductions in incidence during the trial. Realistic adjustments for losses to follow-up are also critical. For CRTs, conservative estimates of the between-cluster variance or intra-cluster correlation should be used.

A reliable assay that could be used to estimate HIV incidence from cross-sectional surveys would be a valuable tool, as this would simplify the task of obtaining reliable prior estimates of incidence for sample size calculations. Development of such an assay that could be widely employed in Africa and other resource-poor settings remains an important research priority.

Improving and measuring adherence

We have already discussed the need to ensure adequate intensity of intervention. For many intervention approaches, this involves assuring participant adherence with the intervention. In some cases, adherence is not an important issue after the initial intervention. For example, the effect of male circumcision is permanent, although it is important that men adhere to

advice not to resume sexual activity until the surgical incision has healed, and there is also concern about the potential for behavioural risk compensation if men (or their partners) think they are completely protected. Depending on the number of doses required, adherence may also be of limited relevance for vaccine trials. However, for interventions such as PrEP or microbicides that require continuous and consistent use of study product, adherence is clearly of central importance.

In prevention trials, careful attention should therefore be given to procedures both to maximise and to measure adherence. Some approaches to improve adherence include frequent visits at which adherence is assessed (for example through pill or gel counts) and adherence counselling is provided; random spot checks to remind participants about adherence; the use of text messaging or mobile phone calls to provide reminders; and the use of electronic devices that record the opening of pill containers.

Because of reporting and social desirability bias, verbal reports of adherence are likely to provide over-estimates of true adherence. Measurement of adherence is likely to be improved if there is triangulation among different approaches to measurement. For example, the MDP301 microbicide trial combined information from case record forms, collection and counting of used and unused gel applicators, self-completed coital diaries and in-depth interviews, to obtain a reasonably robust estimate of adherence [22]. Such estimates are needed in order to apply statistical methods that adjust for compliance during trial data analysis. A consensus set of adherence metrics for each intervention category would greatly facilitate reporting of adherence and meaningful comparisons across trials.

Importance of process measures

We have already noted the value of data on process measures especially for interventions targeting distal determinants of HIV transmission as well as complex interventions with multiple components. Where no effects are seen on primary endpoints such as HIV incidence, process measures can help to assess whether there were aspects of the intervention that were not delivered effectively or which might need to be modified or improved. For interventions targeting distal determinants (Figure 1), data showing effects on intermediate variables in the causal chain can strengthen the evidence of the effectiveness of an intervention as well as elucidating its mode of action. For complex interventions, examination of process measures may provide some evidence of which intervention components played the most important role in producing measured impacts.

CONCLUSIONS

Despite the stabilisation or fall in HIV prevalence seen in some countries in recent years, the HIV pandemic continues to be one of the profoundest threats to global health. Even in countries such as Uganda, which have seen a substantial fall in prevalence, the incidence of new infections continues at an unacceptably high level and in parts of Southern Africa incidence is still extremely high with the lifetime probability of infection exceeding 50% in some populations.

While the roll-out of ART represents a substantial achievement in HIV/AIDS control, and has given new hope to millions of HIV-infected individuals, it has made the need to reduce the incidence of new infections even more pressing. If incidence cannot be reduced substantially, it will become increasingly difficult – logistically and financially – to provide effective care for the ever-expanding number of HIV-infected patients who need it. Given the high cost of ART, effective HIV prevention measures represent an even more cost-effective investment than previously because of the high treatment costs averted.

These observations, combined with the dearth of preventive interventions of proven effectiveness in rigorously conducted trials, point to the continuing importance of HIV prevention research. The large number of flat HIV prevention trials has led some to question the value of continuing investment in this area. We would respond to this with three comments.

First, the HIV prevention score-card, shown in Table 2, is as notable for the small number of published studies as for the high proportion of flat results. Given that we are now 30 years into the global epidemic, and that the severity of the epidemic as a global health emergency has been understood for at least 25 years, it is perhaps surprising that there have been only 39 published trials across all seven intervention categories for prevention of sexual transmission [14]. Commentators have pointed to the high cost of some of these trials, but compared with the global expenditure on HIV control programmes the resources channelled to prevention science have been very limited.

There is little doubt that an expanded evidence-base on HIV prevention methods and a broader array of interventions with rigorous evidence of effectiveness would improve the chances that available resources would be better used for prevention. An important question for investigators and sponsors is whether some trials have incorporated levels of data collection, monitoring and documentation that are a requirement for trials supporting licensing of new products, but which may be excessive for non-regulatory trials.

Second, we have argued in this paper that there are disparate reasons for the flat results seen in HIV prevention trials. In some cases, there are limitations in the design or conduct of the trials that have precluded a useful estimate of effectiveness. In these cases, the solution is not to abandon the intervention, but to ensure that future trials take these considerations into account. In other cases, the trials have given a convincing negative conclusion and these results point to a need to abandon or modify the intervention, or increase the stringency of the selection criteria for future candidates. In some cases, flat results together with carefully collected process data have pointed to new ways of delivering interventions that might be more effective.

Third, there has been a growing tendency to question the role of RCTs in HIV prevention science, particularly for complex prevention approaches involving behavioural or structural interventions. Some interventions, particularly those such as mass media programmes or legal or fiscal measures, may require implementation on such a large scale that randomisation of discrete geographical units is not feasible. Others may act over such a long time-scale and through such an extended causal pathway that evaluation in an RCT may be challenging. Nevertheless, many such interventions can, in principle, be subjected to this type of study using either an individually-randomised or CRT design. The large number of flat results should not be used as an argument for abandoning a well-established research method. Rather, as we have argued above, it should lead us to look either at improvements in the design and conduct of these trials or improvements in the design and implementation of interventions. A well-conducted trial demonstrating lack of effectiveness of an intervention represents a valuable contribution to prevention science, even though the findings may be disappointing. Such trials remain the cornerstone of the evidence needed to support implementation of HIV prevention programmes.

In those cases in which RCTs are not feasible, we must rely on examination of the evidence from rigorously-conducted observational studies, such as large-scale quasi-experimental studies involving comparison of intervention and control areas with careful documentation of relevant baseline data, trends over time and comprehensive process data. Such studies must be carefully designed to maximise their validity [23]. Just as HIV prevention may

require combinations of synergistic interventions, HIV prevention research requires the strategic use of a combination of RCTs addressing the design issues highlighted in this supplement and, when RCTs are not feasible, expanded use of rigorous observational study designs.

We hope that this series of papers provides a useful review of past and ongoing HIV prevention research, and offers new insights into directions for future research. The HIV pandemic is likely to remain one of the major threats to global health, robbing millions around the world of the chance to lead healthy, productive lives. High-quality research is essential to assure a robust evidence-base to help national programmes select the most effective preventive interventions and implement them most strategically in appropriate populations.

POSTSCRIPT

This supplement was finalised shortly before the announcement, in July 2010, of the results of the CAPRISA004 trial of tenofovir microbicide gel, showing a 39% reduction in HIV incidence and 50% reduction in HSV2 incidence among women in South Africa [24]. While confirmatory trials will be needed, this is the first vaginal microbicide to show strong evidence of efficacy and represents an important step forward for HIV prevention research. The HIV prevention score-card (Table 2) should now show 6 out of 40 trials with positive results. The main messages of this supplement remain unchanged.

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Figure 1.

A conceptual framework showing proximate and distal determinants of the sexual transmission of HIV moving from the microbiological/cellular levels (dark grey), through the individual/local community levels (white) to the population/global levels (light grey)

Table 1
Potential intervention targets and approaches to prevent sexual transmission of HIV
across the three levels of the conceptual framework

Target	Examples of Potential Interventions	RCTs completed or ongoing*
Microbiological & cellular levels		
HIV viral load	ART for HIV prevention <ul style="list-style-type: none"> • Pre-exposure prophylaxis • Post-exposure prophylaxis • ART for infected partner • Microbicides 	Yes No Yes Yes
Co-infections	Prevention & treatment <ul style="list-style-type: none"> • Bacterial STIs • Genital herpes • Bacterial vaginosis • Malaria • Tuberculosis • Helminths 	Yes Yes Yes No No Yes
Host defences	Vaccines Male circumcision	Yes Yes
Individual & local community levels		
Sexual behaviours & networks	Risk reduction approaches <ul style="list-style-type: none"> • VCT • Individual, couples or group counselling • Peer education • School-based sexual health education • Skill building • Motivational interviewing • Popular opinion leader interventions • Mass media • Barrier methods <ul style="list-style-type: none"> • Diaphragms • Enhanced condom promotion 	Yes Yes Yes Yes Yes Yes No Yes Yes Yes Yes
Health behaviour & health systems	Partner services Vouchers	No (HIV); Yes (STIs) No
Population & global levels		
Economics	Microfinance Conditional cash transfers	Yes Yes
Socio-cultural	Expanded education for girls	No

* RCTs with HIV incidence as a primary endpoint

Table 2
Summary of findings of randomised trials of interventions to prevent the sexual transmission of HIV

Results of 37 RCTs of 39 interventions to prevent sexual transmission of HIV				
Type of Intervention	HIV prevention efficacy			Total
	Positive	Adverse	No effect	
Behavioral & Microfinance	---	---	8	8
Diaphragm	---	---	1	1
Vaginal Microbicides	---	1	11	12
Male Circumcision	3	---	1	4
HIV Treatment (PrEP)	---	---	1	1
STI Treatment	1	---	8	9
Vaccines	1	---	3	4
Total	5	1	33	39

Adapted from Padian et al, 2010 [14]. Discrepancies between numbers of trials shown in this table and individual reviews in this supplement result from differences in eligibility criteria and classification of multi-component interventions. Not included in this table is the CAPRISA004 trial of tenofovir microbicide gel published in July 2010 which showed a positive effect [24].