Evidence-informed and human rights-based combination prevention combines behavioural, biomedical, and structural interventions to address both the immediate risks and underlying causes of vulnerability to HIV infection, and the pathways that link them. Because these are context-specific, no single prescription or standard package will apply universally. Anchored in ‘know your epidemic’ estimates of where the next 1000 infections will occur and ‘know your response’ analyses of resource allocation and programming gaps, combination prevention strategies seek to realign programme priorities for maximum effect to reduce epidemic reproductive rates at local, regional, and national levels. Effective prevention means tailoring programmes to local epidemics and ensuring that components are delivered with the intensity, quality, and scale necessary to achieve intended effects. Structural interventions, addressing the social, economic, cultural, and legal constraints that create HIV risk environments and undermine the agency of individuals to protect themselves and others, are also public goods in their own right. Applying the principles of combination prevention systematically and consistently in HIV programme planning, with due attention to context, can increase HIV programme effectiveness. Better outcome and impact measurement using multiple methods and data triangulation can build the evidence base on synergies between the components of combination prevention at individual, group, and societal levels, facilitating iterative knowledge translation within and among programmes.

Keywords: combination prevention, HIV, Millennium Development Goal, prevention strategy, structural interventions

Introduction

Although new HIV infections declined to 2.7 million (2.4–3.0 million) in 2008, down from a peak of 3.5 million (3.2–3.8 million) in 1996, HIV prevalence continues to rise. It reached 33.4 million (31.1–35.8 million) in 2008, three-fold higher than in 1990 [1]. With the UNGASS (2001 United Nations General Assembly Special Session on AIDS) decade coming to a close and most countries far short of their UNGASS prevention goals and targets, a serious review of HIV prevention strategies and programmes is underway. Many countries are experiencing important transitions in their epidemics, including in parts of sub-Saharan Africa where evidence of increasing injecting drug use and recognition of transmission among men who have sex with men (MSM) are challenging notions of a solely heterosexual African epidemic.

An estimated 2.9 million lives have been saved in low-income and middle-income countries since triple drug antiretroviral treatment (ART) started in 1996 [1]. Four million people were on ART as of December 2008, representing a 10-fold increase over 5 years [2]. Coverage rose from 7% in 2003 to 42% in 2008, with dramatic increases achieved in eastern and southern Africa (48%) [2]. Recent guidance recommending that ART be started earlier, at CD4 cell counts of less than 350 cells/µl [3], is increasing national calculations of ART need by up to 50%.

Although there is growing evidence of success in HIV prevention in diverse countries [4–5], time is being lost in many others as the epidemic continues to evolve in the absence of adequate responses. Every person who becomes infected eventually requires ART for life and,
daily, for every two people started on treatment, five new infections are occurring. Thus, reducing HIV incidence is critical to keeping the promise of universal access to HIV prevention, treatment, care, and support and to reaching the Millennium Development Goal (MDG) of halting and reversing the HIV epidemic by 2015.

This paper describes how the call for combination prevention became a clarion call. We review the evolution of understanding about HIV prevention, present the consensus definition of combination prevention [6], and outline the ‘know your epidemic, know your response’ strategy, with a focus on sub-Saharan Africa. We conclude with a discussion of tailored programme planning and evaluation challenges.

HIV prevention: the mainstay of the response to AIDS

HIV prevention has been at the core of the AIDS response since the early days when primary prevention was the only life-saving strategy available. From 1988 to 1996, countries applied a range of strategies in their Medium Term Plans, from diagnosis and treatment of sexually transmitted infections (STIs) to HIV education, condom social marketing, policy dialogue, and legal protection for people living with HIV and vulnerable groups [7]. When ART became available, it was widely assumed that it would boost prevention, as people would be more willing to learn and disclose their HIV status and take necessary steps to protect themselves and others from acquiring or transmitting HIV.

Individual agency in HIV prevention

Considerable investments in information–education–communication (IEC) and subsequently in behaviour–change–communication (BCC) strategies resulted by the mid-1990s in near-universal awareness of HIV, with little impact on reported risk behaviour outside sex work and other high-risk settings [8]. Global HIV policy makers began to recognize the need to couple interventions that relied on individual agency with strategies to alleviate vulnerability to infection [9–11]. A decade of disappointing individual-focused behavioural interventions [12] led to calls to re-examine the theories and models of behaviour change [9,13] and consider the societal conditions, such as gender inequalities, sexual cultures, poverty, and access to HIV services, that undermine people’s ability to act on prevention advice. An expanded response to HIV was proposed that would reinforce strategies of risk, vulnerability, and impact reduction [14,15].

Combination prevention enters the scene

Introduced in 2003 as a strategy ‘to use all appropriate interventions to achieve maximum effect, including behaviour change programmes, sexually transmitted disease control, voluntary counselling and testing, harm reduction, prevention of mother-to-child transmission, blood safety, infection control in healthcare, structural interventions, and programmes for people living with HIV’ [16], combination prevention was conceived broadly. It had been inspired by the recognition that countries such as Uganda, Thailand, and Brazil had generated sharp, sustained declines in HIV incidence using an array of biomedical, behavioural, and structural approaches. Visible, consistent, political leadership, and community mobilization seemed critical components of these successful national programmes, each of which had deployed strategically chosen strategies to meet the diverse needs of key populations at risk [17].

For several years, the term ‘combination prevention’ evolved to refer more narrowly to the combination of strategies required to prevent sexual transmission, whereas the term comprehensive prevention applied to prevention programming addressing all modes of transmission. Combination prevention was described as the ‘strategies that informed individuals who are in a position to decide for themselves can choose at different times in their lives to reduce their risk of exposing themselves or others to HIV’, with the limited applicability of such an approach for many women and girls explicitly acknowledged [18]. There was recognition of the need to adapt HIV prevention programming in a balanced approach varying by cultural context, population addressed, and stage of the epidemic and to prioritize policies that would help reduce the vulnerability of large numbers of people by creating social, legal, and economic enabling environments in which HIV prevention is possible [19].

At the global policy level, guiding principles and recommended policy and programmatic actions for intensifying HIV prevention emerged in 2005 [20]. These called for strategic, simultaneous implementation of a combination of evidence-informed policies, and programmatic actions, including biomedical and behavioural approaches, promoting gender equality and protection of human rights, to reduce HIV risk, vulnerability, and impact. Practical guidelines followed in 2007, endorsing locally owned and adapted, evidence-informed HIV prevention strategies founded on respect for human rights and responding to the particular needs of people at highest risk of HIV exposure [21].

These developments occurred against the backdrop of the movement ‘Towards Universal Access’, the focus of the 2006 UN General Assembly High-Level Meeting on ‘Universal Access’ reviewing implementation of the 2001 UNGASS Declaration of Commitment on HIV/AIDS [22]. One hundred and eighty-nine countries endorsed a Political Declaration on HIV/AIDS that called for universal access to HIV prevention, treatment, care, and support. Reaffirming prevention as the mainstay of
the response to AIDS, countries pledged to intensify efforts to ensure implementation of a wide range of prevention programmes that take account of local circumstances and ethical considerations. The signatories committed to overcoming structural barriers to effective HIV prevention – including harmful social, political, legal, and economic conditions that individuals alone cannot change – and ensuring the full enjoyment of all human rights and fundamental freedoms by people living with HIV and members of vulnerable groups [22]. It was a broad agenda linked to regular, visible reporting on progress.

Consensus on defining combination prevention

The need for a combination of biomedical, behavioural, and structural streams of action to reduce HIV vulnerability and risk was underscored at the 2008 International AIDS Society conference in Mexico when Myron Cohen argued that these strategies ‘have been engaged for years; it is time for them to get married – and they should do it today!’ [23]. A series of papers reviewed the history of HIV prevention responses [24] and the state of the art globally on biomedical [25], behavioural [12], and structural interventions [26], highlighting the challenges of designing and managing cost-efficient and high-quality combination programmes at national and sub-national levels [24,25,27]. An accompanying call to action challenged governments, civil society, and researchers to come to terms with complexity and get moving on prevention [28]. As well, the Global Prevention Working Group admonished the scientific, policy, and implementing community to take on HIV prevention more actively [29].

Linking the wave of support for combination prevention that emerged in Mexico with more consistent programmatic action [27], a series of broad consultations defined combination prevention in practical, programmatic terms [6,30]:

Combination prevention programmes are rights-based, evidence-informed, and community-owned programmes that use a mix of biomedical, behavioural, and structural interventions, prioritized to meet the HIV prevention needs of particular individuals and communities, so as to have the greatest sustained impact on reducing new infections. Well designed combination prevention programmes are carefully tailored to national and local needs and conditions; focus resources on the strategic mix of programmatic and policy actions required to address documented risks and needs; and are thoughtfully planned and managed to operate synergistically, strategically, and consistently over time and on multiple levels to address both immediate risks and underlying drivers of vulnerability and risk. They mobilize community, private sector, government, and global resources in a collective undertaking. They require and benefit from enhanced partnership and coordination. And they incorporate sufficient flexibility to permit ongoing assessment and continual improvement of strategies over time [6].

Compared with previous thinking, a broader recognition emerged that structural approaches, that is, public health programmes that promote health by altering the context within which health is produced and reproduced [19,31], are not a nice accompaniment to ‘the real stuff’ of HIV prevention strategies but are central to them [30,32–35]. For two decades, policy makers and advocates ruled out initiatives to change the ‘social drivers’ of HIV risk and vulnerability [35] as falling beyond the remit, and the urgent time frame, of HIV responses. Today, there is a growing desire to apply these principles systematically and consistently in HIV programme planning and implementation. This has been accompanied by greater willingness among policy-makers to budget for structural as well as biomedical and behavioural strategies and among donors to fund them [36–38]. Overall, there is expanding commitment among implementers, researchers, civil society, government, and international partners to be accountable for overcoming the insufficiently strategic approach to HIV prevention that has delayed the achievement of maximum impact [6].

Know your epidemic, know your response and tailored programming

The entry point to combination prevention programming is the ‘know your epidemic, know your response’ strategy [21]. Enabling countries to estimate a single-year ‘snapshot’ of incident infections anticipated over the coming year, the Modes of Transmission (MoT) methodology [39] uses data on current HIV and STI prevalence and behavioural data, including sexual partner types; numbers of individuals with particular exposures, disaggregated by age and sex, and rates of these exposures. Including data points from studies in diverse populations and settings, the model provides a unified picture of the relative contribution to HIV incidence of each examined exposure and, by implication, the relative need for services in various populations. All relevant data from national and sub-national surveys, surveillance activities, behavioural research, participatory mapping studies, rapid assessments, stakeholder consultations, and key informant interviews inform the modelling.

The MoT model shifts attention from where the epidemic has been, as reflected by HIV prevalence, to estimating where the next 1000 infections will arise [39]. Having identified types of risk and exposure and important sub-national variations, the combination prevention approach invites evidence-informed
Injecting drug users
Men having sex with men
Clients of female sex workers
Partners (casual heterosexual sex)

For example, prior to MoT exercises [43], several countries in sub-Saharan Africa had not recognized the extent of HIV transmission or ensured access to appropriate HIV services among MSM [44] or people who inject drugs (Fig. 2). In 2009, Kenya acknowledged that shifts in drug trafficking routes into and across Africa were contributing to its epidemic [45], when its MoT study estimated that 4% of new infections countrywide were contributing to its epidemic [46], rising to 6% in the capital Nairobi. Furthermore, one in six new infections in Nairobi are occurring among MSM, a population that has garnered little prevention programming attention in Kenya. The MoT study in Nigeria led national authorities to conclude that over one-third of new infections are occurring among sex workers, people who inject drugs, MSM, and their sexual partners, indicating the need for greater attention to focused programmes in this generalized epidemic [47]. Likewise, although the majority of new infections in Swaziland and Lesotho are now due to sexual transmission within stable heterosexual couples, prevention programmes have not been directed towards the special needs of serodiscordant couples. Investment in efficient and acceptable ‘know your status’ strategies such as couples counselling [48] and home-based testing and counselling [49–51] can reach this population, previously labelled ‘low-risk’, providing access to treatment which can reduce transmission risk and to prevention strategies adapted to serostatus. In sum, synthesis reviews using MoT modelling lay the foundation for evidence-informed choices on which cost-effective strategies will best meet the current, context-specific needs of those most vulnerable while having the largest population-level impact on epidemic dynamics.

Tailored programming
‘Know your epidemic, know your response’ is the first step, but the choice of an effective, tailored prevention strategy requires both participatory planning and integration of services for synergistic effect. Good participatory practice principles, which apply to the design of tailored prevention programmes just as for the conduct of biomedical HIV prevention trials [52], include respect, transparency, inclusiveness, and accountability. Foundations for efficient use of resources in HIV prevention are the Paris Principles for Aid Effectiveness [53], situating countries in the driver’s seat in national programme planning; the Three Ones Principles [54,55], emphasizing the need for one national strategic plan, one national AIDS authority, and one

Fig. 1. Modes of transmission and gap analysis.

monitoring and evaluation system; and MoT synthesis reviews, supporting countries to focus their programming on current needs.

Adopting and implementing nondiscriminatory and vulnerability-reducing laws and policies and promoting changes in harmful attitudes and social norms are strategies to interrupt transmission dynamics dictated by unfavourable macro-environmental to micro-environmental physical, social, economic, and policy conditions [19,56]. Significant shifts in HIV risk can be achieved through changing specific social norms and other societal conditions, such as gender inequality, HIV-related stigma and discrimination, food insecurity, and violations of human rights. All of these can prevent people from accessing HIV information and HIV services and underpin HIV vulnerability (Fig. 3) [5,57,58]. Programmatic strategies to combat the underlying determinants of vulnerability and risk [5,59–62] begin with engagement of affected communities and systematic situation analysis of the multiple, interacting causes and available levers of change [63]. For example, when the Uganda AIDS Commission analysed the nature and levels of causes of young people's vulnerability to HIV, it consulted with community youth, parents, educators, and service providers [57]. It determined that conditions ranging from cultural norms regarding sexuality and power, to family obligations and expectations, and the quality of available health services needed to be addressed [57]. Securing lasting improvement requires actions on multiple fronts and levels to address coherently the interacting biomedical, behavioural, and structural factors underpinning vulnerability [64].

The recognition that HIV prevention campaigns can and should seek to foster changes in harmful perceptions and social norms was provoked by experts from low-income and middle-income countries who argued cogently that choice-focused behaviour change models, based on secular, individualistic cultures of European descent, had been overemphasized [13]. The rationale for addressing social determinants of HIV vulnerability was further buttressed by the parallel trend of expanding recognition of relationships between health and human rights [65–68]. A promising analytic framework bringing these trends together links state human rights obligations under national and international law with structural-rights interventions to redress societal inequities, reduce vulnerability to HIV, and expand access to treatment [69].

**Novel technologies**

A number of biomedical tools, currently the subject of randomized controlled trials (RCTs), will have implications for combination prevention if they prove effective. Preexposure prophylaxis is being tested in several end-point driven trials that may report results in 2010, with CAPRISA 004 testing a vaginal gel containing tenofovir reporting first. Furthermore, the vaccine field shows promise with the discovery of two powerful antibodies isolated from a developing country donor that neutralize many HIV variants [70] and the finding that a prime-boost combination of two HIV vaccine candidates reduced the risk of HIV infection by about 30% [71]. As already seen following the male circumcision efficacy trials revealing a protective effect of around 60% for heterosexual men [72], knowledge translation into scaled-up programmes can lag behind efficacy trial results. Furthermore, monitoring impact to ensure that novel efficacious biomedical prevention tools are appropriately positioned within combination prevention programming is essential to ensure that these do not displace or undermine other effective strategies and are truly additive. Social change communication and counselling support are integral to the effective introduction of any partially protective biomedical modality, in order to minimize any risk enhancement/compensation subsequent to perceptions of decreased risk.

**Building the evidence base on combination prevention**

The range of research required to evaluate, refine, and cost proven models for all the policy and programmatic actions recommended for a complete prevention response is enormous. Although a variety of frameworks have been proposed [10,11,31,35,73–75], creating and assembling the knowledge necessary to support programme decision-making on all these strategies has never been seriously contemplated as a concrete goal. Understandably, research has focused on strategies to achieve particular biomedical or behavioural objectives, such as reducing reported STI, increasing HIV testing and counselling, or increasing correct and consistent condom use with casual sex partners. However, the combination prevention framework posits that on the ground,
biomedical, behavioural, and structural determinants and outcomes are interlinked.

**Current knowledge**

The science has lagged behind consensus on action for combination prevention. This point is illustrated by the lengthy debate as to what actually led to the decline in Uganda’s HIV epidemic [76,77]. There were records of policy positions, programme plans, and scattered data collection on HIV prevalence and programme performance; however, in Uganda, as in most countries, there was no repository documenting the range of activities and coverage constituting the national HIV programme. An extensive retrospective analysis, using mixed quantitative and qualitative methods in a triangulated approach, concluded that sexual behaviour change began in 1987 with shifts in social norms about concurrent partnerships and postponement of sexual debut, accompanied by increased condom use in the early 1990s [78]. This analysis comes closest to answering ‘what happened in Uganda?’ [77]; however, because key features including government leadership and community mobilization were not measured sceptics may remain unconvinced that structural interventions were essential components of Uganda’s effective response.

There is a substantial body of research measuring the effectiveness of biomedical strategies and testing individually focused behavioural and/or mixed strategies [25–27,79]. In contrast, the evidence demonstrating that specific structural interventions have measurable effects on HIV incidence and other biomarkers, such as STI incidence or pregnancy, is meagre. Seemingly conflicting evidence about the effects of poverty, gender inequality, social capital, and other structural factors has been clarified recently by applying theory and approaches from the social sciences that accommodate the diversity of social, cultural, and epidemiological contexts, the individual agency, and the ‘embeddedness’ and complexity of socially constructed behaviour [32,35,75,80]. These stress the multiplicity of causal pathways connecting broad social and economic factors with individuals’ motivation and capacity to avoid risk [30]. However, the evidence base remains small compared with the scale and diversity of the global challenge.

National AIDS programmes in southern Africa are not waiting for definitive studies with experimental designs. A number of large-scale communication programmes aimed at fostering new sexual norms are underway to discourage multiple and concurrent sexual partnerships in order to bring the region’s explosive HIV epidemics under control [81]. Some conducted baseline surveys to enable programme evaluation in 2–3 years and all began without the benefit of a RCT-tested model. They are ‘learning by doing’, adjusting implementation and developing measurement methods as they go, hoping these will be sensitive and yet comprehensive enough to document inputs, context, and effects.

Changing socially constructed behaviour and social norms is not easy and what works in one culture may or may not work in another. For example, the Popular Opinion Leader model based on theories of diffusion of innovation [82] proved effective in promoting individual reductions in risk behaviour and new HIV and/or STI among diverse populations in the USA [83–85]. When tested in five lower-income and middle-income countries, significant reductions in HIV-related stigmatizing attitudes were found at one site, but changes in risk behaviours or declines in STI incidence did not occur at any site [86].

The relatively thin evidence base on structural interventions poses a major challenge to decision-makers. Diverse definitions of what constitutes a structural approach [10,11,19,35], lack of clarity on the time required for effects and their duration [35,87], and lack of operational guidance [32] have hampered knowledge building. As the focus of structural interventions can be the social, political, economic, or physical environment, and include services, policies, and regulations as well as community processes that catalyze social and political change, it is unlikely that a single conceptual model can encompass all the variables and causal chains at work [10,11,88]. Nonetheless, a common framework would help build the global knowledge and evidence base [35].

In practice, only a few programmes that can be considered to include structural approaches have been reported in the scientific literature. Among them are Sonagachi, a community-oriented project in Calcutta, India, which mobilized and empowered sex worker groups to create an enabling environment, with HIV prevention defined as a community issue [89]. Results of a cluster randomized trial, the Intervention with Microfinance for AIDS and Gender Equity (IMAGE) study conducted in South Africa, revealed no reduction in HIV incidence, but did suggest that microfinance combined with gender and HIV training led to improvements in household economic well being, women’s empowerment, and reductions in levels of intimate partner violence [90], as well as improvements in risk behaviours, increased communication about sex, and greater uptake of HIV testing [91]. The AVAHAN project covering over 80% of the urban female sex worker population in Karnataka, south India, highlights the importance of law, access to justice, and programme scale-up to reach high HIV service coverage among marginalized populations. HIV prevalence did fall among young antenatal clinic attendees, but its link to the programme was unclear [92].

**Building the evidence base**

Building the evidence for what works where, and for whom, in combination HIV prevention can guide programme managers, not only in designing programmes...
but also in selecting appropriate methods to evaluate and iteratively improve them. Three foundational concepts are attention to context, development of a project implementation pathway (PIP), and use of complementary evaluation strategies [93].

At the national level, information on social, cultural, economic, and political context, if collected rigorously, consistently, and preserved over periods of time, can improve HIV incidence modeling and prevention impact assessments [94], as well as the design of programs. A recent think tank, reviewing themes and heuristic tools from research and evaluation science not widely applied in national or sub-national HIV programs [95], concluded that because HIV prevention relies on human behavior and the dynamic meanings, relationships, and societal conditions that shape it, significantly more attention to context is required in program evaluation. Contextual confounders that were not investigated or measured may help explain the weak effects or flat results of recent randomized trials of behavioral HIV prevention interventions [94,95].

Knowing how activities, such as providing HIV testing and counseling or advocating with parliament to abolish discriminatory laws, are expected to contribute to reductions in HIV incidence at the population level is critical. For example, seven different pathways whereby gender inequality may influence HIV outcomes are identified in guidance on implementing the UN Action Framework on Women and Girls [96,97]. Description and understanding of a PIP [98], a highly detailed causal model of how each step in a project is expected to contribute to the ultimate project outcome [99], assists implementers in diagnosing failed assumptions or failing strategies. In Progresa, an RCT of conditional cash transfers as a policy instrument to achieve improvements in maternal and child health and education in Mexico [100], the development of a highly detailed PIP over several rounds of intervention and refinement improved project implementation and impact. Having an explicit PIP is critical to identifying key milestones or intermediate outcomes and to understanding what is and is not working for specific audiences, making needed adjustments, and transferring knowledge to others.

Building the evidence base for combination prevention requires the design and implementation of program evaluation that assess three fundamental axes of program design: is the program meeting the actual needs of the populations most affected; is it being implemented correctly with quality standards maintained, including the meaningful engagement of people living with HIV and avoidance of stigma-enhancing actions; and is it implementing the needed activities on a scale that will make a difference [99]. These questions are often overlooked in studies that aim to evaluate whether an HIV prevention program ‘works’.

Debate continues over the appropriateness from an ethical, feasibility, and utility viewpoint of applying RCT designs, used to evaluate the effects of behavioral and biomedical HIV prevention interventions, to structural approaches which operate nonlinearly and over longer periods [87]. Novel methodologies to evaluate combination prevention, such as stepped-wedge, selective promotion, or adaptive trial designs, are being discussed but experimental and quasi-experimental designs may be both difficult and possibly unethical. Modelling HIV incidence in relation to programmatic inputs, with sensitivity analyses for estimated variables, could answer critical questions concerning likely program impact. Fortunately, strategies are now being developed for teasing out the additive and synergistic outcomes of combination prevention programs, given their flexible, evolving designs. Prospective evaluations of combination prevention programs can use multiple methods and data triangulation, capture unit costs, and take a more complete account of social context and other structural conditions. However, measuring interactions between biomedical, behavioral, and structural components and at individual, group, and societal levels is a key challenge of combination prevention evaluation.

Cross learning as communities and countries undertake much more rigorous evaluation and learn from their own HIV prevention programs will be greatly facilitated if they document their program inputs more consistently using a common language that permits comparison across projects, regions, and countries [30], analyzing inputs in relation to measured or modeled trends in HIV incidence.

Among the newer research initiatives is the US National Institutes of Health ‘Methods for Prevention Packages’ program (MP3) supporting behavioral and biomedical clinical scientists, epidemiologists, and clinical trial design specialists to devise optimal prevention packages of combination interventions for specific populations, design clinical trials to rigorously examine the safety and efficacy of these packages, and demonstrate that the prevention package is acceptable to the target population and that the study design is appropriate and feasible [101]. None of the five initial funded proposals explicitly included a structural component but good participatory practice and further reflection is leading in some cases to recognition of the need for structural interventions to complement behavioral and biomedical components.

The CAPRISA 007 RHIVA trial (Reducing HIV in Adolescents), a cluster randomized trial underway in a very high incidence area of Kwa-Zulu-Natal, is assessing the impact of enhancing educational quality and providing conditional cash transfers to high school learners to reduce HIV incidence. Testing a structural approach at the individual level, much as did the IMAGE microfinance project among women in Limpopo, South
Africa [90], the RHIVA trial secondary end-points include individual academic performance, participation in activities to build confidence in the future, and knowledge of HIV status (Q.A. Karim, personal communication). Addressing the extremely complex, interwoven cultural, social, and economic vulnerability of girls and young women in hyperendemic areas of southern Africa will continue to preoccupy a broad array of researchers and partners long into the future [102].

**Implementation science**

Knowing your epidemic and response is critical in deciding which services to provide to whom, but the new field of implementation science research is needed to address gaps in implementation, strengthening the knowledge base on how to deliver interventions effectively and efficiently, transfer interventions from one setting or population to another, and make informed choices about competing interventions [103]. Although modelling demonstrates that the addition of novel biomedical strategies to an existing prevention package can have synergistic effects, hastening HIV incidence declines [104], programme managers are understandably concerned to ensure that any novel prevention modality makes a net addition to existing efforts. Dialogue with affected communities and monitoring and evaluation, including operations research and programme quality improvement [105] clearly play an important role in improving overall HIV prevention programme effectiveness. Operations research is complemented by broader implementation science research which would, for example, identify barriers to full scale-up of programmes and compare implementation strategies aimed at enhancing uptake to reduce HIV transmission.

**Conclusion**

As the fourth decade of AIDS approaches, primary prevention is more important than ever. Around the world, combination prevention programmes that draw upon the social sciences and community experience, as well as the best of biomedicine, 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. Programme resources focused on evidence-informed, human rights-based, sustained programme and policy actions that reinforce community capacity and resilience [106] will provide good value for money, including benefits beyond the AIDS response. Further, many structural interventions, which seek to reverse social, economic, and physical conditions that undermine the agency of individuals to protect themselves and others, should be instituted regardless because they are public goods in their own right [107].

Because on the ground, the multiple components should be mutually reinforcing, implementation of combination prevention requires an unprecedented level of partnership, collaboration, and enhanced coordination in programme design, resourcing, management, and evaluation. Flexible cyclic designs can incorporate new tools or emerging approaches and allow strategies to evolve in response to epidemiological, social, and technological change, including novel biomedical prevention tools.

Given the diversity of endogenous and contextual influences on HIV risk perception and behaviour in different settings, the search for stable, universal combination prevention models that can be distributed as set ‘packages’ of information and services is futile. It implies lack of appreciation of the social nature of HIV risk and vulnerability, or of the nature of social processes [108]. As Urban Johnsson states, ‘To deal effectively with the diverse HIV epidemic, we do not need more and better patterns so much as we need more and better tailors’ (U. Johnson, 2008, personal communication). Tapping local knowledge and building enduring capacity is especially important as combination prevention entails working with time horizons that stretch beyond short 1–3-year project funding cycles.

After nearly three decades of focus on short-term results, the call for combination prevention recognizes that a mixed approach addressing both immediate risks and underlying causes is both possible and necessary. Researchers, implementers, community members, and policy makers working hand-in-hand across disciplines and national boundaries offer the best hope for meeting the challenge to deliver on the promise of Universal Access and the MDGs. But unless the science of ‘what works where, and why’ expands its base, examining programmes on the ground and using theory and methods from all the sciences, and unless it translates the generated knowledge into dynamic and iterative processes of synthesis, dissemination, exchange, and ethically sound, coordinated application [109], combination prevention will not live up to its anticipated impact in halting and reversing the HIV pandemic.

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