

Combination implementation for HIV prevention: moving from clinical trial evidence to population-level effects

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The promise of combination HIV prevention—the application of multiple HIV prevention interventions to maximise population-level effects—has never been greater. However, to succeed in achieving significant reductions in HIV incidence, an additional concept needs to be considered: combination implementation. Combination implementation for HIV prevention is the pragmatic, localised application of evidence-based strategies to enable high sustained uptake and quality of interventions for prevention of HIV. In this Review, we explore diverse implementation strategies including HIV testing and counselling models, task shifting, linkage to and retention in care, antiretroviral therapy support, behaviour change, demand creation, and structural interventions, and discusses how they could be used to complement HIV prevention efforts such as medical male circumcision and treatment as prevention. HIV prevention and treatment have arrived at a pivotal moment when combination efforts might result in substantial enough population-level effects to reverse the epidemic and drive towards elimination of HIV. Only through careful consideration of how to implement and operationalise HIV prevention interventions will the HIV community be able to move from clinical trial evidence to population-level effects.

Introduction

The term combination HIV prevention has been used to describe the application of many HIV prevention interventions to maximise population-level effects and potentially bring HIV epidemics under control.^{1,2} The landmark results of the HIV Prevention Trials Network trial 052 (HPTN 052),³ a randomised controlled trial (RCT) that showed that antiretroviral therapy (ART) reduces HIV transmission to uninfected partners, established treatment as prevention as one of the cornerstones of combination HIV prevention. These findings came after studies of medical male circumcision (MMC), which reduced male HIV acquisition among circumcised men compared with uncircumcised men in three RCTs.^{4–8} These data, along with findings from studies that showed the effectiveness of condoms and some behaviour change interventions,^{9–17} the potential of pre-exposure prophylaxis for prevention of HIV,^{18–21} and modelling studies that suggested the potential for reversal of the HIV epidemic,^{22–25} provide the impetus to test the effectiveness of combined HIV prevention strategies.

This growing evidence base has led to the initiation of several large-scale combination HIV prevention programmes and trials.^{26,27} However, the success of these efforts will be dependent on the achievement of high sustained uptake as well as the quality of interventions. Although substantial attention has been directed at what should make up the package of prevention interventions for HIV,^{24,26} there has been less discussion of how this package could be implemented—ie, what strategies are needed to achieve broad and sustained population coverage.^{28–31} To succeed in controlling HIV, we propose an additional concept: combination implementation for HIV prevention.

We define combination implementation for HIV prevention as the pragmatic, localised application of evidence-based strategies to enable high sustained uptake and quality of interventions for prevention of

HIV. Combination implementation strategies will be needed to move from trial-based evidence of efficacy to population-level effects.^{32–34} In this Review, we explore potential strategies to be incorporated into combination implementation efforts, focusing first on specific prevention and treatment services and concluding with more cross-cutting issues, and we discuss how these strategies could be used to fulfil the potential of combination HIV prevention in low-income and middle-income countries (LMIC).

Implementation strategies for HIV prevention and treatment

HIV testing and counselling

HIV testing and counselling, the gateway to learning one's HIV status, is a necessary component of all combination HIV prevention strategies. HIV testing and counselling can include pre-test counselling, risk-behaviour assessment, informed consent, and post-test counselling on the basis of test results to provide individually tailored risk reduction messages. HIV testing and counselling alone can offer HIV prevention benefits through reduction of sexual risk behaviours, particularly among HIV-infected individuals.³⁵ Implementation models for HIV counselling and testing can be facility based (either client or provider initiated),³⁶ mobile, workplace based, or home based.³⁷

Facility-based HIV testing and counselling is the standard model in most LMIC; however, use of this model alone has not resulted in high population coverage levels, with most people in LMIC still unaware of their serostatus.³⁸ Community-based mobile HIV testing and counselling, in which the facility typically moves into areas with limited access to HIV testing and counselling, is a promising strategy (table 1). In some populations, this model seems to have provided coverage to about half of the key target groups.⁴¹ Workplace-based HIV testing and counselling also seems to offer an opportunity to increase

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access to this service.⁵⁰ However, definitive coverage levels within a community remain difficult to ascertain with any of these approaches. Furthermore, none of these methods are able to achieve the near (90%) or universal HIV testing and counselling coverage that modelling has suggested is needed for significant decreases in HIV incidence.^{23,24}

Home-based HIV testing and counselling, especially when used in conjunction with point-of-care rapid HIV testing, retains many of the advantages of mobile HIV testing and counselling, but might further improve access to this service and allow more accurate assessment of community-level coverage. Several small-scale to large-scale home-based HIV testing and counselling programmes have been implemented, with high rates of acceptance in both rural and urban communities (table 1). Findings from cost-effectiveness and observational studies have also shown home-based HIV testing and counselling to be a better strategy than facility-based approaches for reaching HIV-infected populations with low rates of previous testing and high CD4 counts—crucial populations to engage for combination HIV prevention interventions.^{51,52}

Because early and comprehensive identification of serostatus is fundamental to the implementation of most HIV prevention interventions, home-based HIV testing and counselling as the primary implementation model might be the most effective of the HIV testing and counselling strategies to achieve high population levels of serostatus awareness. Mobile and workplace HIV testing and counselling seem to offer promising complementary approaches that will be appropriate to some settings. Finally, facility-based testing, in which services are available on an ongoing basis, remains a crucial basic health-care service in most LMIC settings to promote combination HIV prevention.

Linkage to and retention in care

Findings from several observational studies have shown the challenges in engaging people living with HIV across

the entire spectrum of care, both with initial linkage to care and with subsequent retention.⁵³ In a diverse group of HIV/AIDS care programmes in sub-Saharan Africa, only an estimated 59% of patients received CD4 results or were clinically staged after diagnosis⁵⁴ and 25% of patients were not retained in care 1 year after the start of ART.⁵⁵ There are several barriers to engagement, ranging from site-specific transport challenges⁵⁶ to more generalised stigma.⁵⁷ Combination HIV prevention programmes will need to engage a high percentage of the population and address the issues of late presentation for HIV diagnosis and care.⁵⁸

Unfortunately, the evidence base for interventions to link and retain people living with HIV in care remains scarce. Findings from an RCT in rural Uganda showed that involvement of community-based peer treatment supporters decreased the amount of people lost to follow-up by 44% compared with no peer treatment supporters.⁵⁹ In an observational study in Kenya, provision of free cotrimoxazole improved retention of ART-ineligible individuals by more than two times that of historical control individuals.⁶⁰ Integration of HIV treatment services with tuberculosis or primary care services has also shown potential to improve linkage outcomes; for example, an integrated HIV and tuberculosis programme in Uganda increased the proportion of patients initiating ART during tuberculosis treatment from 78% before programme integration to 94% afterwards.^{61–63} However, little evidence exists on how to engage mostly asymptomatic HIV-infected populations with high CD4 counts or how to best identify and engage patients with acute HIV infection. Improved recognition and diagnosis of people with acute HIV infection using such strategies as pooled HIV RNA testing and improving provider awareness might be useful to address this challenging population,^{64,65} but more research in this area is needed.

Point-of-care CD4 testing, which has a growing evidence base validating its use, offers substantial

	Model	Country	Setting	Number tested	Acceptance rate (%)	HIV prevalence
Morin et al (2006) ³⁹	Mobile	Zimbabwe	12 marketplaces	1099	..	29.2%
Grabbe et al (2010) ⁴⁰	Mobile	Kenya	Several provinces	47 539	..	9.0%
Sweat et al (2011) ⁴¹	Mobile	Tanzania, Zimbabwe, Thailand	32 communities	16 129	..	5.9%
Maheswaran et al (2012) ⁴²	Mobile, home	South Africa	One subdistrict	1013 (mobile), 1585 (home)	92% (home)	16.4% (mobile), 18.2% (home)
Matovu et al (2005) ⁴³	Home	Uganda	One district	6602	62%	10.7%
Were et al (2006) ⁴⁴	Home	Uganda	Two districts	2348	99%	7.5%
Negin et al (2009) ⁴⁵	Home	Kenya	One village	1984	62%	8.2%
Kimaiyo et al (2010) ⁴⁶	Home	Kenya	294 villages	90 062	89%	3.0%
Lugada et al (2010) ⁴⁷	Home	Uganda	Five districts	2678	56%	7.1%
Tumwesigye et al (2010) ⁴⁸	Home	Uganda	One district	264 966	94%	4.3%
Sekandi et al (2011) ⁴⁹	Home	Uganda	One urban division	408	69%	7.4%

Table 1: Examples of mobile and home-based HIV testing and counselling models

promise for clinical staging at the time of diagnosis, thus facilitating immediate entry into appropriate care and treatment services.⁶⁶⁻⁶⁸ An RCT of point-of-care CD4 count assessment during HIV testing in South Africa reported an improvement in linkage to care of two times compared with standard of care where patients had to return at a later date for their CD4 results.⁶⁹ In an observational study in Mozambique, there was an 80% reduction in early loss to follow-up compared with patients who had to return for a separate CD4 staging visit.⁷⁰ The implementation evidence base for this maturing technology needs continued validation,^{71,72} and point-of-care CD4 technology development and field trials should be a research priority provided CD4 cell count remains one of the standard assessments of ART eligibility.⁷³ A treatment-for-all model of treatment as prevention, whereby all people living with HIV would qualify for ART regardless of CD4 cell count, is one scale-up strategy that would remove the need for eligibility assessment and obviate much of the need for CD4 testing, but this strategy is not recommended by WHO or most other HIV treatment guidelines.^{23,74}

Although the evidence base for strategies to optimise engagement in care continues to mature, existing programme models that have shown success might provide reasonable starting points for combination HIV prevention activities.^{34,55,59,60,71,75-77} These successful programmes often involve task shifting, decentralisation with community or home-based services, or both, such as in Rwanda where 24-month retention was 92.3% in a community-based programme,⁷⁸ or might incorporate tracking services, such as in South Africa where a patient tracer was able to ascertain the status of 53% of patients lost to follow-up.⁷⁹ Novel community-based programmes with good programmatic outcomes have included self-forming groups of patients in Mozambique, where retention was 97.5% after a median of 12.9 months in care;⁸⁰ the use of handheld technology to successfully support task shifting to people living with HIV in Kenya;⁸¹ incorporation of electronic medical records, which led to a 30% absolute reduction in missed visits due to forgetting in Uganda compared with before incorporation of electronic medical records;⁸² and emphasis of pre-ART care services in Swaziland, which decreased time to initiation of ART from 61 days at baseline to 14 days after introduction of these services.⁸³ Replication of novel approaches and continued innovation and assessment of linkage and retention programmes are needed to further inform this crucial aspect of treatment as prevention.

Treatment support

Patients on ART will need to maintain a high level of treatment adherence for treatment as prevention to be successful.⁸⁴ Implementation strategies to promote and support adherence include the use of peer treatment supporters (also called expert patients, peer health workers, or lay or community health workers), which has

resulted in some improvement in adherence and virological outcomes (table 2). They can also confer survival benefits, as shown in South Africa where mortality was reduced by 62% in patients being monitored by treatment supporters compared with those not being monitored,⁸⁶ although the evidence base remains small. Food support improved adherence by about 50% compared with no food support in a pilot study in Zambia,⁸⁹ but the large-scale implementation and sustainability of such interventions is daunting.⁹⁰ Directly observed therapy studies have had unconvincing results for improvement of adherence, and they remain difficult to scale up at a population level.^{86,91-93}

New technologies have shown promise in supporting ART adherence. Findings from one RCT in Kenya showed that mobile phone alerts coupled with provider support decreased the risk of virological failure by 16% compared with standard of care.⁸⁵ Another Kenyan RCT used a text-message reminder (SMS), which resulted in 13–16% improved adherence compared with standard of care.⁸⁷ However, failure of an alarm device in a third Kenyan study showed how ongoing local assessment of technological strategies is needed⁸⁸ and that reminders alone without patient support might be insufficient.⁹⁴ Additional assessments of electronic reminders and support in other populations would be valuable.

Routine laboratory monitoring does not seem to be an absolute prerequisite for implementation of treatment as prevention, as shown in a trial in Zimbabwe and Uganda in which 5-year survival (87%) and retention (93%) were high in patients who received clinically driven monitoring,⁹⁵ which should be reassuring to people implementing programmes with limited laboratory support. However, laboratory monitoring does have clinical and survival benefits, as shown in rural Uganda, where clinical monitoring alone had 83% higher rates of AIDS-defining events or death compared with viral load monitoring and 49% higher rates compared with CD4 monitoring.⁹⁶⁻⁹⁸ In particular, monitoring of HIV viral load, the best proxy for

	Country	Description of intervention	Number of participants	Outcome summary*
Lester et al (2010) ⁸⁵	Kenya	Text messages with provider support	538	Improved adherence and virological outcomes
Chang et al (2010) ⁵⁹	Uganda	Peer treatment supporters	1336	Improved virological outcomes and reduced number lost to follow-up
Nachega et al (2010) ⁸⁶	South Africa	Treatment supporters and directly observed therapy	274	No effect on virological outcomes, improved survival
Pop-Eleches et al (2011) ⁸⁷	Kenya	Text message reminders	431	Improved adherence, fewer treatment interruptions
Chung et al (2011) ⁸⁸	Kenya	Counselling or alarm device	400	Counselling improved adherence and virological outcomes Alarm had no effect

*In the intervention group compared with the standard of care group.

Table 2: Randomised controlled trials of treatment support interventions

infectiousness at the individual and community level, can have substantial treatment-as-prevention benefits through earlier regimen switching in cases of ART treatment failure and by preventing unnecessary regimen changes, and is invaluable for assessment of drug adherence. For example, findings from a six-country study in Africa showed that 46.9% of switches were unnecessary among patients monitored without viral load testing.⁹⁹ Targeted viral load strategies, in which viral load testing is only undertaken in high-risk patients on the basis of laboratory (eg, CD4 cell count) or behavioural characteristics (eg, adherence assessments), or both, might be initially less costly but needs to be assessed further.¹⁰⁰

Pragmatic application of lay health worker, technology, and laboratory support, tailored to the local epidemic and treatment dynamics, will be needed to assist with implementation of treatment as prevention.^{101,102} Continued assessment of these strategies and their effectiveness in supporting people living with HIV on ART, especially when used in combination, will be enlightening.

Behaviour change and promotion of condom use

Combination HIV prevention will not succeed without substantial and sustained individual-level and community-level HIV risk reduction behaviour change.¹⁰³ One challenge to selection of implementation strategies is the mixed evidence for behaviour change interventions such as individual, couples, and family-based counselling, peer-based strategies, and community-wide methods such as mass media, social marketing, and community mobilisation.^{8–13,104,105} Additionally, disentanglement of the varied contributions of other drivers of HIV incidence from specific changes in behaviour has been difficult.¹⁰⁶ Nevertheless, behaviour change interventions aimed at behaviours such as increasing condom access and use and decreasing sexual partners and activity have had some successes, such as a 33% reduction in risk behaviour prevalence from baseline in those who received risk-reduction counselling in a five-country study,¹⁰⁷ and can be used to guide local implementation approaches. The biomedical intervention arms of HIV prevention RCTs have typically included concomitant behavioural change interventions; a further argument for integrated programmes.

Counselling strategies that address individual risk behaviours and promote condom use have become standard of care for most HIV prevention efforts and they will probably need to continue as foundation components of most combination HIV prevention programmes. In particular, discordant couples are an important population to target for HIV prevention efforts, with couples counselling strategies showing consistent benefits in decreasing risky sexual behaviours in separate studies in Zambia, Tanzania, and Kenya,^{16,108,109} and a programme using facilitated disclosure leading to around 80% rates of disclosure in Uganda.¹¹⁰ Peer

education interventions can play an important part here because they are economical and relatively effective ways to encourage behaviour change.¹⁰⁴ Home-based HIV counselling and testing might also play a crucial part in bringing behaviour change interventions to family settings and difficult-to-access populations. The effectiveness of condoms is well established,¹⁷ and ensuring adequate supply and access will help HIV prevention efforts, although creating demand for condoms and sustaining their use will be difficult.¹² Ongoing assessments of behaviour change implementation strategies are needed, particularly how combination behaviour change interventions (eg, home-based counselling plus mass media) might interact.

Pre-exposure prophylaxis

The evidence base for oral and vaginal pre-exposure prophylaxis continues to increase, with mixed results.^{19–21,111,112} Evidence from implementation science for pre-exposure prophylaxis remains limited because of minimum field experience with efficacious pre-exposure prophylaxis interventions.¹¹³ The reasons for discordant results in some pre-exposure prophylaxis trials remain uncertain, and further analyses will be helpful for the identification of important implementation issues such as the role of adherence in determining intervention effectiveness. Although findings from modelling studies have shown that efficacious and widely implemented oral pre-exposure prophylaxis could result in a cost-effective and significant effect on HIV incidence,¹¹⁴ because of the present uncertainty about population-level effectiveness, oral pre-exposure prophylaxis might not be a core component of most present combination HIV prevention activities. However, in some groups, such as discordant couples where the HIV-infected partner is not on ART or high-risk populations such as sex workers and their clients and men who have sex with men, pre-exposure prophylaxis might play an important part. Demonstration projects of pre-exposure prophylaxis are needed to provide further evidence that this biomedical intervention can be applied at a substantial scale to assist in the control of generalised HIV epidemics.¹¹⁵

Medical male circumcision

In settings of moderate-to-high HIV prevalence and low male circumcision rates, MMC is a crucial component of combined HIV prevention. MMC scale-up has proceeded at variable paces throughout LMIC.¹¹⁶ No RCT evidence was found supporting one type of scale-up strategy versus another. However, several observational studies provide examples of potential approaches (table 3). In South Africa, an effective model of community-based outreach and mobilisation was used,¹¹⁷ and Tanzania's MMC campaign approach exceeded original targets.¹¹⁹ Efforts in Kenya showed substantial early success through government-led task-shifting initiatives.¹¹⁸ Task shifting of MMC seems to be safe, with adverse event

rates similar between procedures undertaken by non-physician clinicians compared with doctors and specialists.¹²⁰

Non-surgical male circumcision devices, such as the Shang Ring (Wuhu Snnda Medical Treatment Appliance Technology, Wuhu, China) and PrePex (Circ MedTech, Tel Aviv, Israel) are undergoing safety and acceptability assessments to identify what part they could play in accelerating MMC scale-up efforts and addressing human resource shortages.¹²¹ These devices are promising and innovative; however, their benefits and adverse effects compared with each other and with surgical methods need to be investigated further. Seasonal demands for MMC—for example, increased demand during school and public holidays—might also need to be taken into account and supply of MMC services adjusted appropriately.¹²² Finally, uptake of MMC among men at high risk of contracting HIV remains suboptimum, and innovative strategies that target this difficult-to-engage population are needed.¹¹⁶

Prevention of mother-to-child transmission

Substantial progress in scaling up prevention of mother-to-child transmission has been made over the past several years.³⁸ New methods of antiretroviral prophylaxis are more efficacious than older methods, but the coverage level remains below target goals.¹²³ Although there are limited published data on the strategies for implementation of prevention of mother-to-child transmission, some approaches have shown promise. These approaches include the use of task shifting, integrating prevention of mother-to-child transmission services into the larger context of care for the mother and family, use of system improvement methods, and empowering mothers to self-administer prevention of mother-to-child transmission.^{124–127}

Combination HIV prevention programmes likely should include prevention of mother-to-child transmission as a core prevention component, not only to reduce HIV transmission to infants, but also to use prevention of mother-to-child transmission as a leverage to increase access to other services for the mother and family.^{127,128} Prevention of mother-to-child transmission serves as a crucial entry point into the health-care system for both HIV-negative and HIV-positive individuals.⁶³ For HIV-negative individuals, the opportunity to access this service increases engagement in care and offers counselling opportunities and seronegative-appropriate interventions. For HIV-infected individuals, various other prevention interventions can be used beyond prevention of mother-to-child transmission, such as ART and couples counselling. Recently, Option B+, a treatment strategy whereby pregnant HIV-infected women are started on triple-drug ART regardless of CD4 count at the time of diagnosis and continue this treatment for life, has gained interest for its clinical and programmatic benefits and might represent a compelling strategic component of

	Location	Key features	Time period	Number circumcised	Estimated coverage
Lissouba et al (2010) ¹¹⁷	Orange Farm, South Africa	Task shifting, single facility	2008–2009	14 011	39%
Mwandi et al (2011) ¹¹⁸	Nyanza, Kenya	Government-led, task shifting, static and mobile sites, diathermy	2008–2011	287 026	50–55%
Mahler et al (2011) ¹¹⁹	Iringa, Tanzania	Task shifting, community mobilisation, facility based	2010 (6 weeks)	10 352	..

Table 3: Models of male circumcision scale-up

prevention of mother-to-child transmission and treatment as prevention efforts.^{129,130} Tight integration of prevention of mother-to-child transmission in combination HIV prevention programmes might therefore have synergistic benefits with other prevention interventions, and careful assessments of the effect of integrated programmes should be encouraged.

Cross-cutting strategies for combination HIV prevention

Task shifting

Task shifting is the rational redistribution of tasks among health workforce teams from higher trained providers to those who need less training.⁷⁶ It is a direct response to the health worker human resource crisis in LMIC, which is a substantial barrier to implementation of combination HIV prevention.^{131,132} Several observational task shifting studies have focused on shifting ART care from physicians to nurses and findings from these studies have typically shown that task shifting can be accomplished without significant differences in quality of care.^{133–137} Several mostly observational studies have also addressed task shifting and MMC (table 3).

Task shifting has been tested in a small number of RCTs (table 4).¹⁴² Findings from a study of home-based HIV care provided by community officers showed that this method of care was as effective as a clinic-based strategy, with similar rates of virological failure.¹³⁸ Home-based care supported by trained people living with HIV resulted in similar patient-oriented outcomes and less frequent clinic visits compared with clinic-based care alone.¹³⁹ Findings from another RCT showed that nurse-monitored care was non-inferior to doctor-monitored care.¹⁴⁰ A recent, large cluster RCT of task shifting care to nurses for both ART initiation and maintenance in South Africa reported no significant differences in mortality or virological outcomes after 16.3 months of follow-up compared with usual care led by doctors.¹⁴¹

Task shifting will be needed beyond service scale-up and should include long-term activities such as adherence counselling and patient support as health systems move towards a more chronic care model for people living with HIV. Combination HIV prevention will also need a complex and large-scale ongoing assessment of individual-level risk factors. Educational and support strategies for less highly trained workers will

need to be strengthened and assessed. Novel approaches to improve worker efficiency and the quality of services delivered might be needed. For example, mobile electronic devices for patient screening and triage to HIV prevention and care have been successfully piloted in Uganda and Kenya.^{81,143} These mobile technologies for health care can be appropriate components of strategies for implementation of combination HIV prevention.¹⁰¹

Because of the scale of the human resource needs for combination HIV prevention, task shifting will be an important component of many implementation activities. Task shifting also represents an opportunity to involve people living with HIV directly in combination HIV prevention activities,¹⁵ including training them as prevention and treatment supporters.¹⁴⁴ The evidence base for task shifting is still being developed, but early findings should be reassuring to implementers who are pragmatically moving forwards with task shifting efforts. Important issues such as maintaining quality, safety, high retention, and developing and maintaining training capacity will benefit from careful monitoring, assessment, and further operational research.^{145–147} Task shifting alone might also not be sufficient to address all the human resource requirements for combination HIV prevention, and a general scale up of provider capacity in LMIC would be ideal.¹⁴⁸

Structural interventions and demand creation

The use of structural interventions such as individual or community-based financial incentives to create demand and uptake of HIV prevention interventions is an area of increasing interest.¹⁴⁹ There have been successes in other specialties with incentive-based programmes.¹⁵⁰ In the specialty of HIV, an RCT in Malawi reported that cash transfer programmes might reduce HIV infections among young women.¹⁵¹ Incentive interventions to increase participation in HIV testing and counselling

have also been successfully piloted.^{152,153} Supply-side strategies such as pay for performance and provider-level and facility-level incentives have shown promise for other health disorders, but assessments of their application to HIV-related interventions remains limited.¹⁵⁴

With a promising but still limited evidence base, the use of financial incentives or compensation for time and travel in combination HIV prevention programmes could be considered, provided that rigorous assessment procedures are concurrently implemented to provide ongoing evidence of effectiveness. An issue of concern is whether compensation should be commensurate with actual costs imposed upon the recipient of the intervention and not constitute an incentive per se for interventions such as MMC. Appropriate compensation might be best calculated by community advisory boards that are familiar with local costs. Structural interventions focused on food insecurity to improve adherence to ART have also shown some effects in pilot studies,⁸⁹ but population-level implementation of food support poses substantial challenges in terms of finance and sustainability.

Increasing the supply of combination HIV prevention services will be inadequate for controlling the HIV epidemic if demand for these interventions is not also increased. Experience with MMC offers some insights into how to create demand. Various community mobilisation strategies in Tanzania seemed to successfully increase demand, with the programme exceeding initial MMC targets.¹¹⁹ Mass communication has also shown some successes in HIV prevention to generate demand.¹⁴ Systematic approaches using mixed methods and economic assessments provide a potential framework for tackling the challenging issue of demand creation.¹⁵⁵ In particular, strategies to involve men in prevention and care activities are needed because men typically have lower levels of ART uptake and higher mortality than women.¹⁵⁶ More rigorous assessments of demand creation are needed with appropriate comparison groups to allow for better assessments of effects.

Key populations for HIV infection

Key populations for HIV infection include, but are not limited to, sex workers and their clients, men who have sex with men, and injecting drug users.¹⁵⁷ The importance of these populations as crucial target groups for HIV prevention efforts is increasingly being recognised.^{158–163} Combination HIV prevention efforts need a “know your epidemic” approach, which acknowledges that these often disadvantaged and marginalised populations might be important drivers of local and national epidemics and might be particularly vulnerable to HIV infection.³³ Modelling the importance of key local epidemiological risk groups in ongoing HIV transmission highlights the importance of targeting prevention interventions for these populations to ensure the success of treatment as prevention.²⁵

	Country	Number of participants	Description	Outcome summary
Jaffar et al (2009) ¹³⁸	Uganda	1453	Care provided by home-based community officers vs facility-based care	No differences in virological or mortality outcomes between groups
Selke et al (2010) ¹³⁹	Kenya	208	Home assessments by people living with HIV vs standard of care	No differences in virological or immunological outcomes between groups. Fewer clinic visits in the intervention arm than in the control arm
Sanne et al (2010) ¹⁴⁰	South Africa	812	Nurse vs doctor monitoring of ART	Non-inferior treatment failure, mortality, and retention outcomes after nurse-led ART compared with doctor-led ART
Fairall et al (2012) ¹⁴¹	South Africa	15 483	Nurse vs doctor management of ART	No differences between groups in mortality or virological primary outcomes

ART=antiretroviral therapy.

Table 4: Randomised controlled trials of task shifting and AIDS care

Various implementation strategies could be emphasised with key populations. The use of needle-syringe distribution for injecting drug users is a proven HIV prevention intervention, but remains largely underused in sub-Saharan Africa and field experience is limited.¹⁶¹ Sex workers would benefit from many interventions suitable for generalised populations but also need some interventions that are specific to their population, such as community mobilisation and empowerment activities.¹⁶⁴ Men who have sex with men are subject to discrimination and barriers to prevention and care access,¹⁶⁵ and outreach efforts and the application of established prevention interventions will be needed.¹⁵⁷ Peers can again play an important part in engaging these groups in prevention and care. However, the evidence base for implementing HIV prevention interventions among key populations in Africa remains sparse, with structural, cultural, and legal barriers impeding efforts to reach these populations.¹⁵⁷ Stigma and human rights violations faced by these populations can greatly impede adoption of HIV prevention interventions, and antidiscrimination laws and ensuring health service inclusiveness are important considerations for comprehensive implementation plans.¹⁶⁶ Efforts to understand the part these groups play in population-level HIV dynamics, and design and investigation of targeted implementation strategies, assessed with appropriate rigorous research designs, should be important components of many combination HIV prevention programmes.

Discussion

In this Review, we have sought to broadly consider various evidence-based implementation strategies that could be incorporated in a combination implementation approach to realise the combination HIV prevention goal of reduced HIV incidence. Several strategies were identified, although the evidence base for many is limited. Furthermore, there is a scarcity of evidence on how best to combine different implementation strategies and what the benefits and trade-offs of different combinations might entail. Nevertheless, sufficient experience exists to guide the early design of combination HIV prevention programmes and trials, and these initiatives will clearly benefit from rigorous implementation science and operational research assessments to inform this rapidly advancing specialty.^{32,34,167} Although randomised study designs will have a substantial role in the investigation of combination implementation and prevention initiatives,²⁶ mixed methods and modelling studies of non-randomised studies will also be of crucial importance.¹⁰⁵

As organisations undergo the process of designing combination HIV prevention programmes on the basis of the available evidence, an initial assessment of local HIV transmission dynamics and resources for HIV prevention and treatment can be helpful in guiding selection of implementation strategies. Programmes will then ideally be developed to reflect these local conditions,

combining the most appropriate prevention interventions with context-specific implementation and operational strategies. Assessment frameworks using mixed methods, iterative processes, and patient-oriented outcomes will be useful to comprehensively assess the effects of these programmes and to inform future efforts. These comprehensive assessments and sustainment of the high uptake of combination HIV prevention interventions will need substantial resources, and the global community will need to make a commensurate financial commitment if these goals are to be realised.

In the assessment of these programmes, the potentially synergistic or antagonistic effects of combining biomedical and behavioural interventions in conjunction with various implementation strategies will need to be carefully considered and monitored. Learning from the benefits and unintended consequences of combination approaches from present programmes and trials will be important. Given the limited evidence that exists for some strategies and interventions, implementers will need to remain flexible enough to alter their approaches as they begin to receive assessment results. The ability to make ongoing, data-driven programmatic course corrections might not just be an advantage of combination HIV prevention efforts, but also a necessity.

This Review has several important limitations. Although a systematic process was undertaken to search for relevant publications, the objective of this narrative Review was not focused on a single strategy or intervention. Narrative reviews are appropriate when broadly summarising a complex, multidisciplinary, and far-ranging topic such as combination implementation for HIV prevention, but might be subject to more biases than systematic reviews.¹⁶⁸ Our literature search was not exhaustive, and other relevant

Search strategy and selection criteria

References for this Review were identified through searches of PubMed, Embase, and the Cochrane Central Register of Controlled Trials with the terms “operations research”, “operational research”, “implementation research”, and “implementation science”, limited by “HIV” and “AIDS” terms without language restrictions. We also reviewed bibliographies of pertinent articles and hand searched high-impact journals in the specialty and authors’ archives. Included papers were those undertaken in low-income and middle-income countries from January, 2000 (around the beginning of the HIV treatment era in low-income and middle-income countries) to July, 2012, which directly assessed an implementation strategy relevant to combination HIV prevention. Systematic reviews and randomised controlled trials were included, as well as observational studies if trial evidence was absent. Conference abstracts were not included. We emphasised in the text those studies most relevant to sub-Saharan Africa—the setting for several combination HIV prevention trials.

evidence on this topic probably exists. Inclusion of articles was based on author judgment about whether an implementation strategy was relevant to combination HIV prevention efforts and might be subject to error or disagreement. The division of the paper into implementation strategies for HIV prevention services and cross-cutting strategies was primarily for didactic purposes, and some strategies (eg, text messaging) could be classified in both sections. In this Review, we sought primarily to introduce the notion of combination implementation and provide an overview of potential components. Further discussions, insights, and research will be needed to more comprehensively explore and better understand the multifaceted issues surrounding these topics.

In summary, HIV prevention and treatment has arrived at a pivotal moment when combination efforts might result in substantial enough population-level effects to reverse the epidemic and drive towards elimination of HIV. For these efforts to succeed, evidence-based combination implementation strategies will need to be concurrently applied, assessed, and refined. The need for rigorous implementation science and operational research to inform combination HIV prevention efforts has never been more urgent.

Contributors

LWC undertook the initial literature searches and wrote the first draft of the manuscript. All authors participated equally in the revision and final approval of this manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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