Large declines in HIV incidence have been reported since 2001, and scientific advances in HIV prevention provide strong hope to reduce incidence further. Now is the time to replace the quest for so-called silver bullets with a public health approach to combination prevention that understands that risk is not evenly distributed and that effective interventions can vary by risk profile. Different countries have different microepidemics, with very different levels of transmission and risk groups, changing over time. Therefore, focus should be on high-transmission geographies, people at highest risk for HIV, and the package of interventions that are most likely to have the largest effect in each different microepidemic. Building on the backbone of behaviour change, condom use, and medical male circumcision, as well as expanded use of antiretroviral drugs for infected people and pre-exposure prophylaxis for uninfected people at high risk of infection, it is now possible to consider the prospect of what would be one of the most remarkable achievements in the history of public health: reduction of HIV transmission from a pandemic to low-level endemicity.

**Background**

Between 2001 and 2012, 26 countries, 16 of them in sub-Saharan Africa, had at least a 50% reduction in new infections. Despite these gains, there were an estimated 1.6-2.3 million new infections in sub-Saharan Africa and 2.3 million globally in 2012. Although scaling up of antiretroviral treatment to the global goal of 15 million people receiving treatment by 2015 is important both to save lives and to contribute to prevention, recent scientific and epidemiological advances provide further support for a more comprehensive prevention strategy.

Combination prevention has been advocated by many and is the application of several evidence-based interventions to achieve maximum effect on population-level HIV transmission in a specific setting. This approach usually entails combination of biomedical, behavioural, and structural strategies. There are no so-called silver bullets. With use of the interventions of combination prevention and a highly focused public health approach—ie, use of available resources for highest population effect rather than individual outcome—a goal of reduction of new infections to move from pandemic levels to low-endemic levels seems within reach. At that level, even a partially effective vaccine, more feasible than the highly effective vaccine, more feasible than the highly effective within reach. At that level, even a partially effective vaccine, more feasible than the highly effective within reach.

**Principles of a public health approach to combination prevention**

Although scientific advances now provide a range of interventions with proven clinical efficacy, challenges remain in translation of these advances to population-level effectiveness. The concept of combination implementation has been introduced to capture the need for pragmatic, localised application of evidence-based combination prevention strategies to enable high, sustained uptake and quality of interventions in a real-world setting. The US President’s Emergency Plan for AIDS Relief (PEPFAR) has also presented its blueprint to create an AIDS-free generation. In addition to relevant services and strategies already introduced elsewhere, we offer a set of key principles of a public health approach to support policy makers in the complex business of combination implementation—a process requiring judgment and best guesses on what might work, or what some might call the art of public health.

**Epidemics are not uniform: focus on high-transmission geographies and key populations**

Much heterogeneity exists in levels of HIV prevalence and incidence between and within geographical regions, and by age, sex, and risk-taking behaviours. These vast variations suggest that a particular focus on high-incidence locations will probably achieve the greatest gains.

The 12 countries with highest prevalence made up more than 40% of estimated new infections globally in 2012.1
Panel: Key elements of combination prevention

**Behaviour change**

**Efficacy and effect**

- Decreases in population-level prevalence and incidence correlated with reductions in risk behaviour in several highly affected countries

**Key issues**

- Difficult to attribute population-level changes to specific programmes
- Self-report bias limits interpretation of behavioural data
- Reductions in risk among young people not replicated in older cohorts
- Overall population prevalence reductions can mask high prevalence among key populations

**Condoms**

**Efficacy and effect**

- Consistent use reduces incidence by 80–95%
- Condom promotion has been shown to be a successful intervention to reduce transmission among key populations such as sex workers

**Key issues**

- Barriers remain to reaching high levels of condom use
- Use is often inconsistent and sporadic (e.g., use at last sex <20% in many high-prevalence countries)
- Condom use can be particularly low in stable, long-term partnerships
- Difficult for women to negotiate use; limited uptake of female condoms with early designs but increased with newer products and marketing

**Voluntary male medical circumcision**

**Efficacy and effect**

- Reduces female-to-male sexual transmission by 60% or more; protection increased over time
- Life-long partial protection
- Estimated 3.4 million infections averted from 2011 to 2025, if coverage scaled up to 80% in 13 priority countries
- Nearly half of projected infections averted by 2025 are expected to be among women

**Key issues**

- Low uptake in many countries despite reasonably high acceptability
- Human resources, cost, infrastructure, and political issues remain
- New non-surgical devices and traditional and political leader support will be important
- Risk compensation could negate benefits; however, no evidence in initial studies
- Observational studies in men who have sex with men are inconsistent

**Antiretroviral therapy (ART)**

**Efficacy and effect**

- 96% decrease in transmission among stable serodiscordant couples with early initiation of ART
- Strong empirical and modelled evidence that ART can reduce transmission at a population level

**Key issues**

- Decreases in prevalence in some countries predated scale-up of ART
- Increased prevention programmes limits sole attribution of decreases in incidence to ART
- Increasing incidence despite high ART coverage in some settings (e.g., Uganda, and men who have sex with men in the USA and Amsterdam)
- Effect of ART in young people in whom infection rates rapidly decreasing requires study
- Treatment cascade poses challenges—e.g., average CD4 count at ART initiation is well below 350 T cells per μL in high-income, middle-income, and low-income countries; 40% of serodiscordant couples decline early ART

**Pre-exposure prophylaxis (PrEP)**

**Efficacy and effect**

- Efficacy ranges from no effect to 44% in men who have sex with men, 39% in women who used topical PrEP, and 75% in discordant couples

**Key issues**

- Achieving and maintaining high levels of adherence is essential
- Potential for drug resistance is concerning; no evidence of PrEP-induced resistance in trials; models predict lower rates of resistance than from ART, because of prevention effect
- Many cost and implementation issues

**Prevention of mother-to-child transmission**

**Efficacy and effect**

- Combination ART reduces cumulative transmission at 6 weeks to 3.3%

**Key issues**

- Need a focus on improvement of coverage, quality of services, and monitoring

**Harm reduction**

**Efficacy and effect**

- A package of needle exchange, substitution therapy, and ART decreases transmission in injecting drug users
- Reduction of unmet need estimated to have large effect—e.g., a decrease in HIV prevalence by 41% in Odessa (Ukraine), 43% in Karachi (Pakistan), and 30% in Nairobi (Kenya)

**Key issues**

- Several political and policy issues remain in many settings
Within countries HIV prevalence often varies greatly between provinces or states, and even between districts. In Kenya, for example, there is a 15-fold difference in prevalence between the highest-prevalence and lowest-prevalence province.\textsuperscript{76} Countries defined as low prevalence (<5%) often have areas with high prevalence (>10%). Incidence can also be highly variable. For example, incidence in young women aged 15–19 years in South Africa’s KwaZulu-Natal region is 4–7 per 100 person-years, compared with a national incidence of 1–49 per 100 person-years.\textsuperscript{77} Even within severely affected areas of rural South Africa one in three new infections can be attributed to clustered so-called hot zones, comprising only 5–7% of the area studied.\textsuperscript{78} In Lesotho, some such hot zones have a prevalence among men of more than 35%, whereas other areas in the same district have a prevalence of less than 6%.\textsuperscript{79} Despite an overall national adult prevalence of 3.1% and incidence of 0.36–36 per 100 person-years, geographical variation in incidence across Nigeria’s large population, including five states with prevalence of about 10%, contributed to an estimated 260,000 new infections, or 11.3% of global numbers in 2012.\textsuperscript{1}

Drivers of each epidemic and microepidemic can differ greatly, even in the same country. In addition to data for age-specific and sex-specific prevalence that remain strikingly similar in countries with generalised epidemics, drivers of a specific epidemic must be examined to determine high-risk populations. In some cases, there will be overlap between high-transmission geographies and high-risk groups. In others, people at high risk for HIV—eg, sex workers, men who have sex with men (MSM), young women, or people who inject drugs—can be dispersed throughout a region with a low average rate of HIV incidence. In Kenya, for example, serodiscordant couples contribute an estimated 44% of new infections, but in Nairobi and on the Kenyan coast, MSM, including those in prison, represent about a fifth of new infections and are emerging as a population in need of urgent intervention.\textsuperscript{76} In South Africa, an estimated 9–2% of all new infections are related to MSM, and 19–8% are related to sex workers.\textsuperscript{77}

Risk taking is not distributed equally in any population. Those engaging in specific behaviours that put them or their partners at risk for HIV infection cluster geographically and socially. Because of this combination, the individual behaviour alone does not determine the extent of new infections, but the location and mixing patterns also greatly increase—or reduce—the chance that the virus will be transmitted.

Despite continued promotion of a “know your epidemic, know your response” agenda by UNAIDS, and previous calls for and emphasis on hot zones,\textsuperscript{75–77} focus on high-transmission regions and populations most at-risk of new infection remains challenging.\textsuperscript{79} Regular and high-quality epidemiological data need to be collected and reviewed, and people at high risk must be identified, informed, given access to treatment, and remain adherent to programmes. These challenges can be compounded by marginalisation, stigmatisation, and criminalisation of key populations.\textsuperscript{80–82} It can also be difficult for countries to commit resources and programmes to specific geographical areas, particularly in ethnically diverse countries. From a human rights perspective, there is a solid case to be made for equitable access for all interventions.

Notwithstanding these challenges, identification of people at high risk for HIV, providing them with access to information and interventions, and maintenance of high levels of adherence are essential for prevention strategies to have an effect. A focus on high-transmission regions and key populations is essential for cost-efficient use of scarce health and community systems and financial resources, and can be the foundation to achieve sufficient coverage of, and adherence to, intensive community-based interventions with links to health delivery services to substantially reduce incidence. Although care and treatment must be equitably provided, prevention interventions, including aggressive use of test and treat (eg, in areas of very high transmission or for groups of people most at risk, treating irrespective of CD4 T-cell count) or treatment as prevention (TasP) where appropriate, should be directed where they will have the greatest effect. Indeed, focused implementation might advance equity and human rights for all by reducing the overall risk of new infections. In some nations with small populations and high rates of infection—eg, Botswana and Swaziland—focus on geography and most vulnerable population could include the entire country.

**Design a package of interventions most likely to reduce transmission in each microepidemic**

Once high-transmission areas and key populations have been identified, the elements of the prevention toolbox with the greatest potential to be effective, acceptable, and deliverable can be chosen. Consistent with the approach set out in the UNAIDS 2011 Strategic Investment Framework,\textsuperscript{83} these considerations will span biomedical, behavioural, and structural forms of intervention.

To maximise the prevention effect of the interventions delivered with the resources available, the programme must be carefully calibrated to the local epidemic conditions and take account of prevailing costs. Mathematical modelling provides a precise way to synthesise data for epidemiology, behaviours, interventions, and costs to guide how this can be done.\textsuperscript{84} Generally, model analyses have suggested that, with the prevention options available nowadays, greater financial resources can translate into greater effect on the epidemic.\textsuperscript{84–86} Thus in the highest incidence hotspots, increased investment and the use of new prevention technologies could yield substantial gains in reduction of the level of the epidemic in a country overall.

For example, in a hotspot area where transmission within stable serodiscordant couples is a key source of
new infections. programmes might leverage existing programmes for HIV testing and prevention of mother-to-child transmission (PMTCT) to identify discordant couples and prioritise prevention services according to their specific needs. In addition to condom promotion, male circumcision could be offered to the male partner if he tests negative, and immediate initiation of antiretroviral therapy (ART) can be offered to the positive partner, and pre-exposure prophylaxis (PrEP) to the negative partner if ART is not initiated or until the positive partner achieves complete viral suppression.

By contrast, in settings where more transmission occurs in young women in casual partnerships, screening methods that identify and reach women at highest risk (eg, those out of school or engaged in transactional sex) can be packaged with use of PrEP for HIV-negative women, increased access to ART—even including a test and treat approach in areas of very high transmission—and promotion of condoms and voluntary male medical circumcision (VMMC) in men. When a key driver of continued transmission seems to be the large age difference between young women and older male partners under circumstances of poverty, gender-based violence, and lack of education, behaviour change programmes must be customised to prioritise key vulnerable subgroups of the young female population. Where they have increased negotiating capacity, sex workers should be a group to promote condom use to, as well as offering access to PrEP and support for increased access to ART including test and treat in areas of very high transmission. In an MSM-driven epidemic, focus on earlier identification and access to treatment including test and treat in areas of very high transmission, condom promotion, and PrEP might be considered.

Models have been an indispensable resource to shape policy and planning programmes because they can show how programme inputs can translate into effect and costs. But models alone are not sufficient. Sometimes, the total cost and feasibility of a project will be more important than whether or not a strategy is strictly the most cost effective. Planners can also identify synergies and antagonisms between programmes relevant to their communities that models do not capture. For example, provision of a wide range of choice in prevention options can, in itself, help to increase uptake of services in the same way that increased method mix is now valued within a family planning context globally. In other settings, sharp discontinuities in the provision of services between adjacent areas, although perhaps optimal, might not be feasible.

Use a critical path to structure and evaluate intervention programming
The use of a critical path, or the sequence of events needed to achieve an outcome, with key performance indicators, can help to streamline public health policy making while promoting greater management efficiency of programmes. For example, a critical path for a new product analyses the key steps from clinical development, regulatory approval, policy and advocacy, and delivery, including structural or legal barriers that limit access and finance across a predicted timeframe for rollout.

Development of a critical path for each intervention to be used in each hyperendemic region or population could be valuable for ministries of health and implementing partners. As one looks across the pathways, some common denominators will be identified. For example, testing is necessary for PMTCT, PrEP, TasP or test and treat, and even VMMC. Antiretroviral drugs are needed for PMTCT, PrEP, and TasP or test and treat. One might also begin to identify various common outlets for services. For example, serodiscordant couples could be identified in antenatal clinics, family planning clinics, and schools (at an age that is culturally appropriate) that could then also be used as entry points for intensive promotion of condoms, partner reduction, VMMC, PrEP, and TasP or test and treat. Similar outlets could be as, if not more, useful to identify young women at risk.

Local epidemics require local solutions: use feasibility studies and acceptability research
In recounting the effort to eradicate smallpox, as much weight has been put on understanding of local cultures and norms to avoid mistakes and promote vaccination as on the medical intervention itself. Uptake of any health intervention, and particularly those involving both intimate human behaviours such as sexual practices and marginalised populations, is likely to be affected by non-clinical factors rather than clinical trial results. In addition to individuals who might access services, feasibility studies and market research can help to understand the views of key constituencies—eg, HIV-positive people, health providers, faith leaders, tribal or other local leaders, community-based organisations, and all segments of civil society that can affect uptake. Feasibility studies and market research has been used successfully for condom use, introduction of vaccines, and other areas. However, they have not been used systematically, nor do they seem to have gained currency as essential components of successful combination prevention.

The success of any health intervention requires engagement well beyond the traditional health sector, and is even more important when stigma, discrimination, sexual violence, and other societal norms play a substantial part. To effectively reach key populations and control HIV, far more engagement of communities and civil society is essential. Although advocacy and civil society engagement have been essential elements of the fight against HIV, as biomedical interventions become more prominent, there seems to be a tendency to focus on a health system that ends at the clinic. For combination prevention and implementation to succeed, we believe that the health system should be viewed as extending deep into the community.
Feasibility studies to assess cultural issues and acceptability related to interventions can include the following: factors that could promote acceptance of HIV testing; optimal delivery routes for various interventions; preferences for and options to promote uptake, use, and adherence of interventions; preferences and concerns about various combination prevention interventions that might be available; and potential for risk compensation and ways to minimise it.

Acceptability studies help to gauge demand for existing health interventions, but can also be forward leaning. In studies of PrEP acceptability, questions about longacting injectable or vaginal products were included.104 Although results from clinical trials and regulatory approvals are several years away,109 understanding of long-term preferences can assist policy makers to begin planning for incorporation of new products as they become available, potentially shortening the timeline from clinical trial results to real-world application. Combining acceptability studies also saves time and money in duplicating this analysis for each new product.

Situations change: regularly assess drivers of epidemics and assess effectiveness of interventions

HIV epidemics are not stagnant. In eastern Europe, the epidemic has begun to shift from intravenous drug users to the wider population.100 Transmission hot spots—within and between countries—can also shift, with some areas achieving relative control while others are recalcitrant or even increasing. The drivers and geographies of epidemics in each country should be regularly assessed to ensure that combination prevention strategies can be maximally effective. No one indicator or data element might be sufficient. Case reports, surveys (eg, prevalence of antenatal clinics, population surveys), and special studies (eg, behavioural and treatment uptake assessments) are all useful. The use of a critical path can also assist to assess progress. Therefore, it is essential that countries collect relevant data, and that UNAIDS and WHO regularly report on subnational geographical prevalence and incidence estimates as well as estimates for those most vulnerable and key affected populations.

Ultimately, it is necessary to assess the effect of interventions based on HIV incidence. The present gold standard is the nationally representative Demographic Health Survey (DHS). However, DHS can be undertaken only every 3–5 years,101 and prevalence data collected can only indirectly be used to calculate incidence from successive surveys. Investments in HIV prevention activities aiming to reduce incidence urgently need an improved quick, easy, valid, and precise method to estimate incidence in populations to guide prioritised interventions.102 UNAIDS has suggested periodic estimations of HIV incidence and modelled number of infections averted by particular programmes.103 Others have suggested use of trends in HIV prevalence among young people as a proxy for incidence (but that addresses only one risk cohort),105 randomisation of different combination prevention strategies in different areas to assess effect.106

Beyond development of an incidence assay, general improvements in surveillance and evaluation are valuable to guide a strategic response. PEPFAR has used public health evaluations and an implementation science framework—the study of methods to improve the uptake, implementation, and translation of research findings into common practice within its programmes to improve their efficiency.107 This type of implementation science can be used to assess the relative efficacy and cost-effectiveness of components—eg, the most cost-effective way to identify serodiscordant couples.108 Advances in statistical analysis might help to evaluate the elements of a package that are synergistic or antagonistic, multiplicative or additive, and to establish the population effect of HIV interventions.

Demonstration projects for new interventions can help to assess effect and maximise efficiencies before expansion to larger implementation. Similarly, studies of earlier identification and access to treatment for key populations at high risk are under development in some countries in the hope of learning these lessons about early treatment. This approach can be usefully extrapolated to a broader combination prevention context to gain better understanding of the effective interplay of various intervention components in priority populations before national scale-up. Assessments are often viewed as luxuries and are the first to be cut. This view is shortsighted. The rapidly changing nature of HIV demands regular assessment and adaptation to ensure maximally efficacious and cost-effective combination prevention. At the same time, collection of data for the sake of it is cost inefficient. It is necessary to identify the key areas for assessment during the planning phase and to resist the temptation to continually add indicators and increase the frequency of collection. However, assessment must be understood as an integral part of any combination prevention strategy.

Data are powerful if collected and presented in ways that policy makers understand, and if data are proactively gathered to meet their needs. In our collective experience, data following the principles presented would promote effective policy making at global, and more importantly, national level. Strong leadership will be integral to make difficult decisions in both design and implementation of combination HIV prevention programming in resource-constrained settings.

Conclusion

In our view, scientific research has identified the methods to develop combination programmes that could control the HIV pandemic. But there is a short window of opportunity that must be acted upon. As seen in the first
few years of the 21st century in sub-Saharan Africa as a whole and the mature epidemic in Uganda, as well as in key populations in the USA and Europe. Decreases in new infections can be fleeting and incidence can rise despite substantial increases in national ART coverage rates. If we do not seize the opportunity now, and we see recent progress reverse and HIV rates again on the rise, control might be beyond our reach fiscally and epidemiologically.

A focused public health approach that prioritises hyperendemic and high-endemic hot zones and key populations and individuals with the combination of interventions that are most likely to have high effect in the most cost-effective way could achieve one of the greatest accomplishments in the history of global health—conversion of the HIV pandemic, the deadliest of the modern era, to a low-endemic level. Now is the time to act.

Contributors
AJ did the literature review, wrote the first and subsequent drafts, responded to reviewer comments, and prepared the final draft. IC did the literature review, reviewed the first draft, provided reference materials, contributed to writing subsequent drafts, and assisted in responding to reviewer comments. FA and JJ did the literature review and contributed to writing drafts. PC, NK, and HR reviewed earlier drafts and contributed to data interpretation. TH did the literature review on modelling, reviewed drafts, contributed to writing, and assisted in responding to reviewer comments. KO contributed to the original idea behind this manuscript, provided reference materials, reviewed drafts, and offered specific text for inclusion. FK and BS reviewed earlier drafts and contributed to writing. BdZ reviewed drafts, contributed to writing and interpretation, and contributed to framing by leading the UNAIDS initiative to define combination prevention. Jj and SK did the literature review and reviewed drafts. JH did the literature review and assisted in proofreading. PP contributed to the original idea behind this manuscript, reviewed earlier drafts, and contributed to writing subsequent drafts, drafted and finalised the response to reviewers, and finalised the manuscript.

Declaration of interests
We declare that we have no competing interests.

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