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ORIGINAL RESEARCH ARTICLE

Health Economics Research on Non-surgical Biomedical HIV Prevention: Identifying Gaps and Proposing a Way Forward

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Abstract

Background and Objective Although HIV prevention science has advanced over the last four decades, evidence suggests that prevention technologies do not always reach their full potential. Critical health economics evidence at appropriate decision-making junctures, particularly early in the development process, could help identify and address potential barriers to the eventual uptake of future HIV prevention products. This paper aims to identify key evidence gaps and propose health economics research priorities for the field of HIV non-surgical biomedical prevention.

Methods We used a mixed-methods approach with three distinct components: (i) three systematic literature reviews (costs and cost effectiveness, HIV transmission modelling and quantitative preference elicitation) to understand health economics evidence and gaps in the peer-reviewed literature; (ii) an online survey with researchers working in this field to capture gaps in yet-to-be published research (recently completed, ongoing and future); and (iii) a stakeholder meeting with key global and national players in HIV prevention, including experts in product development, health economics research and policy uptake, to uncover further gaps, as well as to elicit views on priorities and recommendations based on (i) and (ii).

Results Gaps in the scope of available health economics evidence were identified. Little research has been carried out on certain key populations (e.g. transgender people and people who inject drugs) and other vulnerable groups (e.g. pregnant people and people who breastfeed). Research is also lacking on preferences of community actors who often influence or enable access to health services among priority populations. Oral pre-exposure prophylaxis, which has been rolled out in many settings, has been studied in depth. However, research on newer promising technologies, such as long-acting pre-exposure prophylaxis formulations, broadly neutralising antibodies and multipurpose prevention technologies, is lacking. Interventions focussing on reducing intravenous and vertical transmission are also understudied. A disproportionate amount of evidence on low- and middle-income countries comes from two countries (South Africa and Kenya); evidence from other countries in sub-Saharan Africa as well as other low- and middle-income countries is needed. Further, data are needed on non-facility-based service delivery modalities, integrated service delivery and ancillary services. Key methodological gaps were also identified. An emphasis on equity and representation of heterogeneous populations was lacking. Research rarely acknowledged the complex and dynamic use of prevention technologies over time. Greater efforts are needed to collect primary data, quantify uncertainty, systematically compare the full range of prevention options available, and validate pilot and modelling data once interventions are scaled up. Clarity on appropriate cost-effectiveness outcome measures and thresholds is also lacking. Lastly, research often fails to reflect policy-relevant questions and approaches.

Conclusions Despite a large body of health economics evidence on non-surgical biomedical HIV prevention technologies, important gaps in the scope of evidence and methodology remain. To ensure that high-quality research influences key decision-making junctures and facilitates the delivery of prevention products in a way that maximises impact, we make five broad recommendations related to: improved study design, an increased focus on service delivery, greater community and stakeholder engagement, the fostering of an active network of partners across sectors and an enhanced application of research.

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Key Points for Decision Makers

HIV remains a serious global public health challenge. While the prevention landscape has expanded considerably in recent years, with many new products in the pipeline, evidence suggests prevention technologies do not always reach their full potential. Health economics evidence at key decision-making junctures, particularly in early development, can help identify and address barriers to the uptake of future products.

With the aim of better informing these decision-making junctures, we carried out a mixed-methods study to identify current gaps in health economics research of HIV prevention. We found substantial gaps in scope in terms of study settings, populations and technologies, as well as in modalities of service delivery. Further, we also found important methodological gaps, including a lack of emphasis on equity, heterogeneity, dynamic use of technologies over time, uncertainty and complexity.

In order to better inform the development and uptake of future products, we make five broad recommendations related to: improved study design, an increased focus on service delivery, greater community and stakeholder engagement, the fostering of an active network of partners across sectors and an enhanced application of research.

1 Introduction

It has been 40 years since the first cases of HIV were reported. While great strides in HIV prevention have been made globally, the search for effective, affordable and usable biomedical HIV prevention technologies continues. For years, male condoms were the only prevention technology available to prevent sexual transmission of HIV. In the late 1980s and 1990s, evidence confirmed their effectiveness in preventing HIV [1, 2], followed by efforts in the 2000s to improve their availability and use [3]. In the early 2000s, a second condom was introduced, the female condom, which some thought would revolutionise HIV prevention for women [4]. However, decisions early in the development process, such as the use of polyurethane, contributed to a low uptake. As such, the female condom was subsequently felt to be less desirable to the male condom on key attributes such as ease of insertion and removal and fit and feel during intercourse [5]. It also had higher costs [6] and lower levels of promotion and availability [7]. More effective assessments of the potential impact of these factors during early development stages could have led to an improved product design.

A decade later, phase III trials of an antiretroviral-based vaginal microbicide gel showed efficacy of 54% among women who consistently used the products, but overall trial efficacy was limited (39%) generally attributed to poor adherence [8]. While efforts to improve gel-based prevention have yet to succeed at scale, antiretroviral-based technologies have since shown greater promise. In the 2010s, oral pre-exposure prophylaxis (PrEP) was identified as being highly efficacious in the prevention of HIV [9–11]. Nevertheless, many challenges remain, such as suboptimal uptake and adherence related to a range of structural factors such as stigma and costs [12], which contribute to variable use and, consequently, impact. Evidence suggests that barriers have prevented technologies from reaching their full potential despite the advancement of HIV prevention science over the last four decades.

A number of innovative new technologies are becoming available or are in the development pipeline: from implants in pre-clinical stages to multipurpose prevention technologies (MPTs) in phase III clinical trials [13] to the vaginal ring recently receiving regulatory approval [14]. An increasing array of these products will likely be available for use at scale in the near future. Critical health economics evidence at appropriate decision-making junctures could help identify and address potential barriers to product development, introduction and uptake of future HIV prevention products.

The body of health economics evidence to inform key decisions for the use of new biomedical prevention technologies is growing. However, gaps remain both in the scope of available evidence and in the methodological approaches used to answer critical research questions related to the cost effectiveness, acceptability and potential impact of new products. Consequently, this paper aims to identify key evidence gaps and propose health economics research priorities for the field of non-surgical biomedical HIV prevention.

2 Methods

This project was implemented using a mixed-methods approach and following a convergent design [15] with the three distinct components described below and summarised in Fig. 1. The gaps and priorities identified through these complementary efforts were consolidated and analysed, forming the basis for recommendations proposed in this paper. Further details on the methods used can be found in Appendix 1 of the Electronic Supplementary Material (ESM).

In all components, we focus on biomedical prevention technologies and exclude condoms and surgical approaches such as voluntary medical male circumcision. While condoms and voluntary medical male circumcision have been proven effective and cost effective in preventing HIV

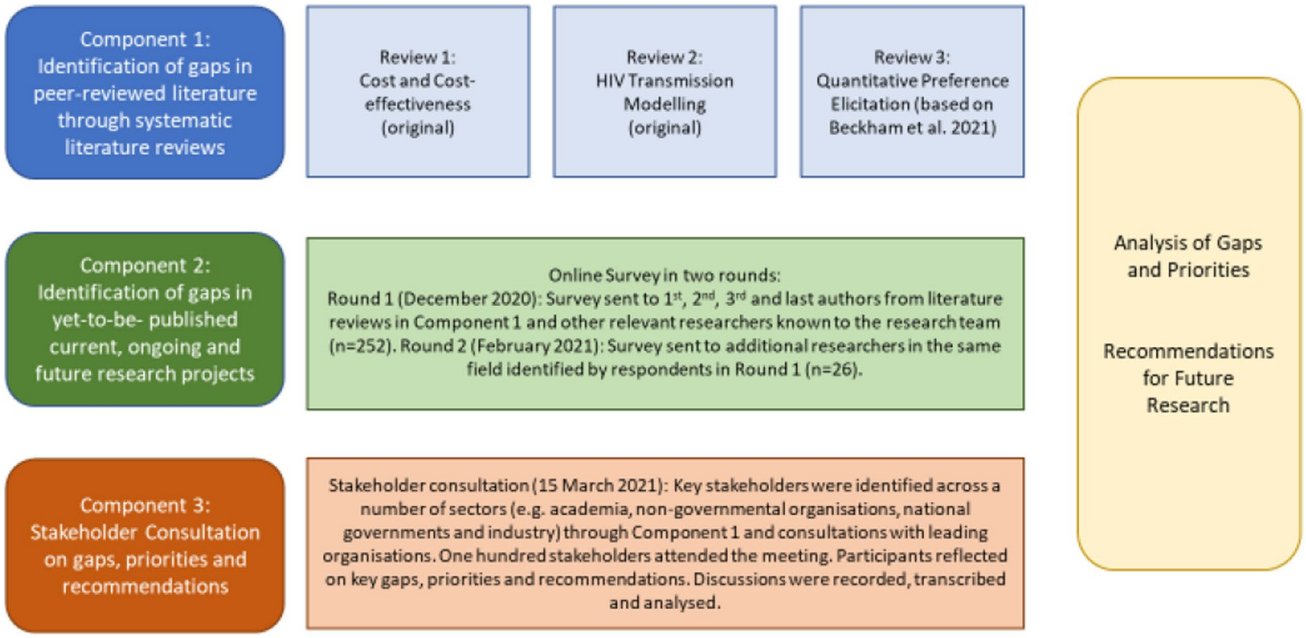

Fig. 1 Summary of study components

acquisition, generating quality evidence on non-surgical biomedical interventions is more urgent given existing knowledge gaps and the number and range of technologies in the pipeline [13].

2.1 Systematic Literature Reviews

We captured peer-reviewed literature through systematic reviews of published research on non-surgical biomedical HIV prevention technologies across all country income levels in three health economics areas deemed relevant to inform the research, development and roll out of new technologies: (i) costs and cost effectiveness; (ii) HIV transmission modelling; and (iii) quantitative preference elicitation. We chose these three areas because they can inform distinct and sequential decision problems. Quantitative preferences research can provide information about product and delivery attributes that can influence development of a technology. Transmission modelling gives estimates on the number of infections that are likely to be averted, which are essential in understanding the value for money of products, an important consideration around pricing and adoption. Lastly, cost and cost effectiveness also provide information necessary to understand value for money and additionally can inform on the affordability of introduction and the budgetary needs for scale up.

We conducted original reviews in areas (i) and (ii) that can be found elsewhere [16, 17]. For (iii) we used a recent systematic review conducted by Beckham et al. on quantitative preference elicitation research for HIV prevention [18] as the basis for our analysis. The scope of that review was broader than ours and included other types of HIV prevention interventions (e.g. condoms). With permission, we drew on their literature search and conducted a sub-analysis on papers relevant to our study.

In all three reviews, data were extracted on study characteristics and study methods. Data on study findings were also extracted, although these varied by review type: (i) costs and cost-effectiveness outcomes; (ii) model characteristics; and (iii) quantitative preference results. Data were analysed using descriptive statistics and a thematic analysis. The quality of each paper was assessed using relevant guidelines [19–23]. Greater details on the methods, including an overview of inclusion and exclusion criteria and quality assessment, can be found in the published reviews [16, 17] and in Appendix 1 of the ESM.

2.2 Survey

In order to map yet-to-be-published recent, ongoing and future research projects, we carried out an online survey with researchers working on the economics of HIV prevention. Participants were identified among the authors of the papers retrieved in the aforementioned literature reviews and through our team's own networks. The survey was conducted in two rounds (December 2020 and February 2021). A total of 278 researchers were directly contacted and invited to participate. The survey asked a series of

descriptive questions about study characteristics (e.g. population and technologies studies) and study methods used (e.g. cost-effectiveness analysis) for recently completed and ongoing research, as well as plans for future research. At the end of the survey, respondents were encouraged to forward the survey link to other researchers working in relevant fields. We analysed the data using descriptive statistics.

2.3 Stakeholder Consultation

An online stakeholder consultation with key global and national players in HIV prevention, including experts in product development, health economics research and policy uptake, was held in March 2021. The aim of the consultation was to obtain further views on gaps in research on the health economics of HIV prevention technologies, as well as to elicit views on priorities and recommendations for the field.

The consultation included a presentation of the findings from the systematic literature reviews and survey [24], a panel discussion with speakers from key sectors, followed by facilitated discussion in small breakout groups and a larger collective group. The meeting, including breakout sessions, was recorded. The research team listened to the recordings several times and made comprehensive notes ensuring that all points made by all participants were captured accurately. Notes were analysed thematically by the research team in an iterative manner. Further information on the meeting approach and agenda can be found in Appendices 1 and 2 of the ESM.

Survey respondents and participants in the stakeholder meeting received an information sheet and were asked to consent to participating in this study. Ethical approval for this study was obtained from the Research Ethics Committee of the London School of Hygiene & Tropical Medicine.

3 Results

In this section, we summarise findings from the systematic reviews, followed by results from the survey and, finally, findings from the stakeholder consultation.

3.1 Systematic Literature Reviews

Out of a total of 3928 papers identified, full texts for 145 peer-reviewed papers were reviewed and their data were extracted. While the three systematic literature reviews address different areas of health economics, some similarities can be found across the literature. Studies largely focussed on low- and middle-income countries (LMICs) with a particular emphasis in Southern and Eastern Africa. The majority of studies focussed on oral PrEP. While overall there was evidence on both general population and key populations, emphasis on the populations studied varied according to country income categories and the health economics area. Most work on key populations focussed on men who have sex with men (MSM) and female sex workers (FSW).

3.1.1 Cost and Cost Effectiveness

Eighty-seven costing and cost-effectiveness studies were retained for analysis, including 20 studies that were also retained for analysis in the HIV transmission modelling review below (see Appendix 3 of the ESM for a list of articles found in both reviews). The full results of the cost and cost-effectiveness systematic review are found elsewhere [16].

Approximately two-thirds of studies focussed on LMICs, particularly on South Africa (31%) and Kenya (10%). Most studies (56%) analysed interventions targeting the general population. Of those looking at key populations, most focussed on MSM (44%), although largely in high-income countries (HICs), followed by FSWs (10%). Most studies (80%) focussed on oral PrEP regimes. Of these, 48% were conducted in Eastern and Southern Africa and 46% in Western Europe and North America. Of the studies looking at HIV vaccines (13% of all studies), 55% were conducted in Eastern and Southern Africa, and 27% in Western Europe and North America. Fewer than half of the retrieved studies provided details on delivery platforms (43%); those that did largely assumed delivery through traditional delivery methods (e.g. vertical HIV programmes). Only three studies focussed on integration with other services [25–27].

The majority of studies were economic evaluations (80%), of which most were cost-utility analyses (55%), allowing for comparisons of cost effectiveness across disease areas. Most studies used a provider or payer perspective (86%) (vis-à-vis a societal perspective). Most studies also calculated economic costs (90%) (which account for the opportunity costs of all resources used) rather than financial costs (which only reflect actual expenditure). Studies calculating economic costs are more amenable to economic evaluations rather than budgeting purposes. Few studies contained primary data (10%), while most used secondary cost data and disease transmission models. A minority of studies (30%) included above-service level costs (i.e. costs pertaining to activities including support services provided by central administration, such as a central laboratory services, and ancillary services that support specific interventions, such as training, education, and outreach and demand generation

campaigns). Study quality was high overall, although information on sampling frame, type of units used and uncertainty were often missing.

Daily oral PrEP was generally found to be costly, with the potential of being cost effective (i.e. representing good value for money in specific settings) at lower prices for the drug or when targeting key populations: nine studies found that PrEP programmes targeting the general population in LMICs would not be included in an optimal package of prevention services, which would rather favour scaling up existing interventions, such as universal or early antiretroviral therapy (ART) and voluntary medical male circumcision [28–36]. Time-limited PrEP was found to be cost effective during pregnancy and breastfeeding [37]. Four studies found that 'on-demand' PrEP was cost effective in both the general population and MSM in high- and upper middle-income settings, where PrEP prices are higher [38–41], as well as among partners of migrant workers in a low-income setting [42]. Some evidence suggests cost effectiveness is sensitive to PrEP adherence, risk compensation and ART coverage. The cost effectiveness of HIV vaccines remains unclear; most studies assume high impact (even if imperfectly efficacious), although much uncertainty remains around vaccine costs. Three studies in an HIC setting suggest vaccines could be highly cost effective compared with oral PrEP among MSM, but not among the general population [43–45]. Evidence on microbicide gels, injectable PrEP and vaginal rings suggested that assumed prices are currently too high for these technologies to be cost effective outside of vulnerable groups, even in settings with a generalised epidemic, like South Africa [27, 35, 36].

3.1.2 HIV Transmission Modelling

Forty-three studies were retained for analysis, including 20 that also appear in the cost and cost-effectiveness review. The full results of this systematic review can be found elsewhere [17].

Most studies focussed on LMICs. The majority of those covered Southern and Eastern Africa, and in particular South Africa (23%) and Kenya (14%). Most studies from HICs focussed on MSM, whereas the largest proportion of studies from LMICs, nearly half, focussed on heterosexual populations. The majority of studies modelled the impact of PrEP (93%), in particular oral PrEP, although many did not specify the formulation modelled. Twelve percent modelled the impact of vaccines and one paper modelled broadly neutralising antibodies.

Thirty unique HIV models were identified. Only one used a stochastic approach (which accounts for randomness within probability distributions and therefore leads to a range of possible outputs) [46]. Most models used deterministic approaches, which do not take randomness into account and so outputs are more directly related to specific parameter values and assumptions. The vast majority of studies modelled sexual transmission, with a small proportion of studies (7%) exploring other modes of transmission (e.g. sharing of intravenous needles or vertical transmission). The quality assessment suggested that, while models used in a majority of studies (58%) were deemed appropriate for answering the research questions posed, many (40%) were found partially appropriate because of oversimplification of disease progression, insufficient regard for heterogeneity or the omission of ART use. Gaps in reporting demographic data and uncertainty ranges were noted. A small proportion of studies (12%) validated their predictions with other available data.

Uptake and drop-out rates were common parameters in PrEP models, although many studies did not account for adherence (65%). Papers often stratified different population groups (85%) to analyse the impact of targeting PrEP to subpopulations. A limited proportion of models (27%) incorporated the impact of PrEP on drug resistance levels and an even smaller proportion (7%) considered risk compensation. All vaccine models made assumptions with respect to efficacy owing to the lack of available evidence while vaccines remain in development. In vaccine models, numerous scenarios were used to represent vaccine uptake, including different roll-out schedules and approaches (continuous vaccination vs mass vaccination campaigns). Many vaccination models failed to consider drop-out for those requiring repeat doses (60%). Some models (7%) incorporated a targeted vaccination of subgroups. Other gaps identified included models unsuccessfully incorporating the efficacy of multiple interventions when acting in combination, not considering key subgroups for analysis (e.g. ethnicity), and ineffectively incorporating intricacies surrounding personal preference and risk perception.

3.1.3 Quantitative Preference Elicitation

Beckham et al. identified 6944 citations and retained 84 studies for analysis [18]. From those, we included 35 studies in our analysis pertaining specifically to non-surgical biomedical HIV prevention. Full results can be found in Appendix 4 of the ESM.

Sixty percent of studies were conducted in LMICs, and 40% in Western and Central Europe and North America. In HICs, similar proportions of studies were conducted with the general population and key populations, primarily MSM and people who inject drugs. In LMICs, most studies were conducted with key populations, especially MSM, FSW and transgender women. Most studies (63%) measured preferences for only one technology, with 43% focussed on oral PrEP, followed by microbicides (34%), injectable PrEP (29%) and vaccines (26%). Seven studies explored dual

protection of PrEP against sexually transmitted infections and unintended pregnancy.

Nearly half of studies reviewed used a conjoint analysis (51%), whereby participants were presented with alternative scenarios with a combination of product or service delivery attributes included in each scenario and asked to rank or rate the scenarios by preference. Twenty-eight percent of studies reviewed used willingness-to-pay and willingness-to-accept methods, followed by discrete choice experiments (17%), where participants were presented with multiple choice sets of alternative scenarios and asked to select their preferred scenario for each choice set. Nearly all studies measured preferences for product-related attributes, most commonly: efficacy, form of technology and price. Fewer than one-third of studies assessed attributes related to service delivery, including dispensing location, dispensing frequency and waiting time. Evidence on preference heterogeneity by behavioural and social characteristics was limited. Most studies reported using convenience sampling (77%), while random sampling (11%) and respondent-driven sampling (3%) were rarely applied. On average, studies were assessed to be of average quality with most studies providing a sufficient explanation of methods, using representative samples and employing appropriate statistical methods.

The evidence on preferences for PrEP varied by formulation. Two studies, conducted with vulnerable populations in Latin America and Southern Africa, suggested higher preference for on-demand over daily use, while three studies, also conducted with vulnerable populations in both Latin America and North America, showed no strong preferences [47–52]. Similarly, preferences for injectables over oral, gel or suppository formulations varied between studies, with participants in five out of ten relevant studies expressing a strong preference for injectables across a range of country income levels and populations [52–56]. High efficacy was often reported to be important across populations, but particularly among vulnerable groups, such as MSM, FSW and transgender women [47–51, 57–61]. There was an overall positive preference toward longer protection, dual protection against HIV and unintended pregnancy, low costs and minimal side effects. Willingness to pay (from a payer perspective) varied by setting and population but was higher among wealthier and employed respondents, as well as those who perceived themselves at a higher risk [58, 62, 63]. Studies carried out with a range of populations, including MSM and FSW, in different regions reported preferences for PrEP collection outside of ART clinics although there were conflicting preferences on whether PrEP should be obtained with or without a prescription [52, 53, 64]. In terms of future vaccines, studies (all carried out in North America) found no strong preferences for dosing frequency [65–68]. A preference for higher vaccine efficacy was reported among general populations and vulnerable populations in North America and Asia [66–72]; one study in Thailand showed a higher willingness to pay (from a payer perspective) between vaccines with 95% efficacy over those with 50% efficacy [72]. A longer period of protection and no side effects were preferred across settings and populations. Two studies, both carried out in Asia, found no strong preferences for vaccine delivery location (e.g. private vs public health facilities) [69, 71]. Two studies, both in LMICs, reported a willingness to pay for the vaccine that ranged between 2008 US$220 and 2002 US$670. Willingness to pay was higher among wealthier and married respondents and those who perceived themselves to be at high risk [72, 73].

3.2 Survey

We received responses from 57 individual respondents (maximum response rate of 21%). Twenty respondents (35%) did not report relevant recently completed or ongoing projects. The remaining 37 respondents (65%) listed a total of 53 relevant recently completed (31%) and ongoing (69%) projects, which were retained for analysis. Most respondents represented universities in HICs. Most recently completed and ongoing projects focussed on HIV transmission modelling (41%) followed by cost and cost-effectiveness analyses (33%), and quantitative preference elicitation (13%). Most studies were carried out in Southern and Eastern Africa (60%), with South Africa (15%) and Kenya (15%) being most frequently represented. No studies were reported for the Middle East and North Africa or Eastern Europe and Central Asia. The most studied population was MSM (22%), followed by the general population (21%) and FSWs (15%). Seventy-seven percent of recently completed and ongoing research focussed on PrEP (77%).

Slightly over half of individual respondents (53%) stated they were planning future health economics research in HIV prevention technologies. Cost and cost-effectiveness methods were the preferred approach (43%), followed by HIV transmission modelling (33%) and quantitative preference elicitation (16%). Most respondents (63%) stated that future research would focus on oral and injectable PrEP; 9% stated future work would focus on vaginal rings and 9% on MPTs. See Tables 1 and 2 and Fig. 2 for a breakdown on settings, populations and technologies reported. Full results from the survey can be found in Appendix 5 of the ESM.

3.3 Stakeholder Consultation

One hundred stakeholders from a range of sectors attended the consultation (see Table 3 for a breakdown of stakeholders by sector). Stakeholders discussed a range of gaps in health economics research of non-surgical, biomedical HIV prevention technologies including, but not limited to, those identified in the (i) literature reviews and (ii) survey. A

Table 1 Survey results: studies (recently completed and ongoing) broken down by region

Region	Percentage of studies
Eastern and Southern Africa	61
Asia and Pacific	17
Western and Central Africa	8
Latin America and the Caribbean	7
Western and Central Europe and North America	7

Table 2 Survey results: studies (recently completed and ongoing) broken down by population

Population	Percentage of studies
Men who have sex with men	22
General population	21
Female sex workers	15
Adolescent girls and young women	10
Other	10
Transgender people	7
Adult women	7
Infants	3
Sero-discordant couples	3
People who use drugs	2

complete meeting report can be found in Appendix 2 of the ESM and we summarised the main findings below.

3.3.1 Population, Geographies and Technologies

Participants advocated for expanded research in neglected populations including pregnant people, people who breastfeed, transgender women and people who inject drugs. Further, the importance of understanding the preferences of community actors such as 'community enablers and gatekeepers' (including partners, peers, policymakers and providers) who can influence the social acceptability of, access to and uptake of products was highlighted. Participants called for inclusion of diverse geographies, including a greater number of countries within sub-Saharan Africa, and other LMIC regions. They also highlighted the need for a broader focus on non-sexual modes of transmission, including through vertical and intravenous transmission. While there continue to be substantial gaps in evidence on some prevention technologies (e.g. broadly neutralising antibodies and implants), recent research platforms are starting to close the evidence gaps on prevention options for women, including vaginal rings, injectable products and MPTs [74].

3.3.2 Service Delivery

Participants noted a lack of evidence on service delivery. While most research is conducted on traditional service delivery settings (e.g. facility-based delivery), there is a lack of evidence on the cost structure of above-service delivery costs, and on the cost and impact of key ancillary services (e.g. demand creation, stigma reduction, awareness raising and social marketing), which can drive cost effectiveness. Participants called for an increased focus on non-traditional delivery models, including decentralised methods, telemedicine and private pharmacy-based delivery, as well as identifying preferred delivery pathways for diverse vulnerable groups, including evidence on strategies for integration between HIV prevention and other care-seeking areas.

3.3.3 Complexity

Current health economics research does not often capture the complexity of care-seeking practices and sexual behaviour. Studies often fail to acknowledge individuals' evolving prevention needs over the course of their lifetime, including switching between technologies, and preferences for short-term and on-demand uses (e.g. post-exposure prophylaxis) according to risk. Further, participants emphasised the need for greater efforts to account for the broad and evolving context of product choice, including models that consider multiple interventions simultaneously, cost-effectiveness analyses that use a range of comparators, and studies on effectiveness, uptake and trade-offs of a greater range of products.

3.3.4 Methods

Participants also highlighted a number of methodological gaps, chief among them a lack of consideration for equity. Enhanced efforts to understand the types of products, service delivery models and ancillary services that will contribute to more equitable outcomes for vulnerable groups are urgently needed. A greater use of complementary approaches to cost-effectiveness analyses (which generally prioritise efficiency in resource allocation) was also highlighted. Distributional or extended cost-effectiveness analyses and inclusion of behavioural economics research could help bridge potential gaps between cost effectiveness, financial risk protection (i.e. the ability of people to access healthcare services without risking financial hardship) and equity. Greater steps are also needed to account for diverse preferences for technologies and delivery mechanisms in key population groups and geographies, particularly in marginalised communities. Further, greater efforts should be made to ensure that evidence reflects 'real-world' implementation. Too often, studies use data from small-scale studies, pilots or trials that do

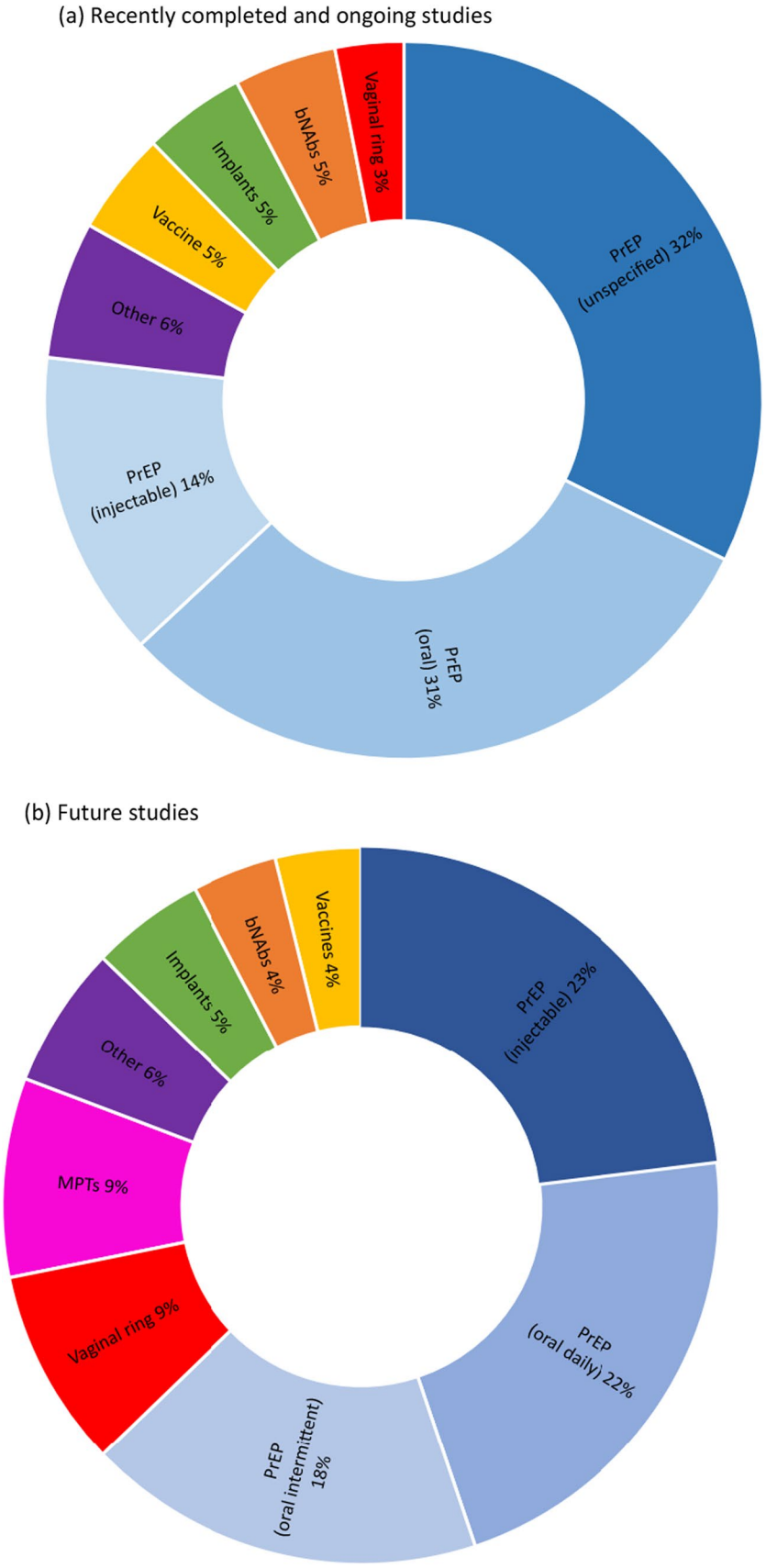

Fig. 2 Survey results: studies broken down by prevention technology. **a** Recently completed and ongoing studies and **b** future studies. *bNAbs* broadly neutralising antibodies, *MPT* multipurpose prevention technologies, *PrEP* pre-exposure prophylaxis

Table 3 Attendees of the stakeholder meeting by sector

Sector	Number of attendees
Academia	32
International organisations	17
Donor organisations	14
Research organisations	9
Consultancy and technical assistance organisations	7
National governments	7
Non-governmental organisations	7
Patient and advocacy groups	4
Industry	3
Total	100

not reflect implementation realities in specific populations at scale. Revisiting trial-based and modelled projections once interventions have been scaled up could improve the quality of evidence used in decision making.

3.3.5 Evidence Interpretation

At a broader level, there is a lack of clarity on outcome metrics (e.g. cost per disability-adjusted life-year averted, cost per infection averted) and their appropriateness for different policy decisions, as well as limited consensus on adequate cost-effectiveness thresholds. Some participants proposed wider use of alternative decision rules or approaches rooted in national budgets, reflecting what individual countries can afford and are willing to pay under specific constraints.

3.3.6 Policy Relevance

Finally, participants noted that research questions and methods are often not responsive to specific or useful policy questions. For example, cost-effectiveness analyses often do not directly convey the financial implications of new technologies by including budget impact analyses. Additionally, analyses often do not consider the perspectives of diverse payers (e.g. donors vs national governments vs individuals), the impact of cost sharing or patient costs, which may hinder access to new technologies. For a summary of identified gaps across the three components of our study, see Fig. 3.

4 Discussion

We collected data on key health economics evidence gaps for non-surgical biomedical HIV prevention technologies through three systematic literature reviews, a survey and a stakeholder consultation. The three methods were complementary: the literature reviews allowed us to map and analyse existing research, the survey provided a glimpse into research that will be in the public domain in the near future, and the stakeholder meeting provided a broader synthesis and critique of the body of evidence from a number of different perspectives, including academia, international organisations, user groups, national governments, donor organisations and industry, as well as validating and refining priorities and recommendations.

Despite the large body of existing evidence in the health economics of HIV prevention, we identified important gaps in scope and methodology. Comparatively little research has been carried out overall on certain key populations (e.g. transgender people and people who inject drugs) and other vulnerable groups (e.g. pregnant people and people who breastfeed), as well as MSM in sub-Saharan Africa and adolescent girls and young women in low- and middle-income settings outside of Africa. Research is also lacking on community actors who influence acceptability and uptake of technologies, as well as on providers and policymakers. While oral PrEP has been studied in depth, other promising technologies have been neglected, including non-oral PrEP formulations (e.g. implants, vaginal rings and injectables), broadly neutralising antibodies, MPTs and post-exposure prophylaxis, although upcoming research may fill some of these gaps. Intravenous and vertical transmission have also been understudied. A disproportionate amount of evidence on LMICs comes from two countries (South Africa and Kenya). Evidence from other countries in sub-Saharan Africa as well as other regions is needed, particularly West and Central Africa, the Middle East and North Africa, and Eastern Europe and Central Asia. Further, data are needed on costs and impact of non-traditional service delivery modalities, integrated service delivery, ancillary services, as well as above service-delivery cost structures.

Key methodological gaps were also identified. There is a lack of focus on equity and heterogeneity. Current research rarely acknowledges complex and dynamic use of prevention technologies over time, including switching between technologies and short-term use, and changing risk perceptions and profiles. Greater efforts are needed to collect primary data, quantify uncertainty, systematically compare the full range of prevention options available and validate trial, pilot and modelling data once interventions are scaled up. There is also a lack of clarity on cost-effectiveness outcome measures and appropriate thresholds for policy decisions. Lastly, research often fails to reflect policy-relevant questions and approaches.

4.1 Recommendations

The collective findings from these three research components informed the development of five overarching recommendations for future health economics research for the field

Fig. 3 Summary of gaps identified through literature reviews, survey and stakeholder consultation. *bNAbs* broadly neutralising antibodies, *MPTs* multipurpose prevention technologies, *MSM* men who have had sex with men, *PEP* post-exposure prophylaxis, *PrEP* pre-exposure prophylaxis, *PWID* people who inject drugs

of non-surgical biomedical HIV prevention. We encourage researchers and practitioners to critically engage with our recommendations and build on them in their respective fields.

4.1.1 Improved Study Design

Recommendation 1: Improving equity in access and outcomes will require additional complexity in research, a better understanding of individuals' choices, further exploration of heterogeneity of preference and behaviour, and greater efforts to gather cost data that is disaggregated, comparable and transferable between settings, as well as a move toward understanding packages of technologies in a context of user choice.

Driving toward more equitable outcomes will require improved understanding of the life courses of individuals and how risk perceptions and profiles, access points, preferences, demand and utilisation considerations, ancillary services and related cost inputs of heterogeneous groups change over time. Studies should explore heterogeneity more systematically and along a number of characteristics including gender, socioeconomic status, race, geographical region and sexual orientation, as well as risk and behaviour profiles. However, addressing equity in health economics research efforts will also require greater clarity on how equity is defined and careful consideration of the trade-offs between equity, efficiency and effectiveness. Greater alignment is needed on which types of equity analysis and data inputs are appropriate in different research contexts.

Better quality primary data outside of trial and pilot programmes, as well as expanded costing efforts, will be important for economic evaluations across heterogenous populations. If a more diverse set of costing inputs cannot be collected, improved frameworks for extrapolating findings across groups and contexts are required. Currently, generalisability of findings is hindered by methodological divergence and setting-specific data and assumptions. Simple and clear transferability frameworks are needed to strengthen comparability across contexts and studies so that when evidence is lacking, data from one setting can more effectively be used to inform policy changes in other settings [75, 76]. Studies should be designed in a manner that makes the process of adapting evidence across settings and populations more transparent. Greater data disaggregation should be encouraged. Furthermore, it is important to validate predictive models using empirical data.

Additionally, there is an overall need to increase complexity in research projects both in terms of scope and methods. As the range of technologies expands, and the product

landscape increasingly changes to one of user choice, it is important for research to account for user engagements with multiple technologies and to capture dynamic user preferences over time. This may translate into policy questions that move away from an emphasis on the cost effectiveness of single technologies but that rather examine mixes of technologies over time and account for user preference shifts. It is also important to embrace more holistic strategies that blend socio-behavioural analyses, demand assessments and economic evaluations.

4.1.2 Impact of Service Delivery

Recommendation 2: Research needs to go beyond traditional service delivery and explore the health economics of alternative service delivery models, costs for above-service delivery, service integration and ancillary services, as well as health system constraints.

Economic evaluations are often incorporated as an adjunct to trials or small-scale pilot interventions, which often limits their ability to capture holistic product and service delivery strategies or to accurately reflect 'real-world' considerations informing product introduction and scale up. Should studying products at scale be unfeasible, collecting primary data on key inputs applicable across different types of products (e.g. disaggregated delivery costs by health system level) would be useful for more refined cost-effectiveness modelling.

Research on service delivery should engage with user choice and preferences more explicitly, taking into account heterogeneity, and should identify preferred delivery pathways for diverse vulnerable groups in order to improve equity. Exploring the health economics impact of integrated and non-traditional strategies of service delivery (e.g. decentralised methods, telemedicine and private pharmacy-based delivery) is a priority. Lessons learned from service delivery adaptation in response to the coronavirus disease 2019 pandemic (e.g. large-scale implementation of telemedicine) could be leveraged to improve understanding of the cost effectiveness and preferences for alternative pathways of service delivery, as well as create resilient strategies for the future.

Research is also needed on the health economics of ancillary services (e.g. demand creation, stigma reduction, awareness raising and social marketing), as well as above-service delivery costs. Both costs and effects of these interventions should be explored, with a particular emphasis on exploring effects on equity. It is also important to capture integrated and inter-related packages of interventions more comprehensively, while acknowledging health system constraints and resources required to relax them. While costing in these areas is methodologically complex, some funders, such as the US President's Emergency Plan for AIDS Relief (PEPFAR), the US Agency for International Development (USAID), the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), and the Joint United Nations Programme on HIV/AIDS (UNAIDS), are already paving the way by contributing to the development of guidelines, including on Activity-Based Costing and Management (ABC/M), and producing rich costing data using this approach [77]. Furthermore, PEPFAR has led resource alignment work to link accounting systems so that service delivery, above-site and programme management budgets and expenditure can be jointly mapped across PEPFAR, Global Fund and national governments [78]. Further work is needed to leverage, link with and expand upon these ongoing efforts.

4.1.3 Community and Stakeholder Engagement

Recommendation 3: Community-centred research is needed in vulnerable populations and neglected geographies, which will require greater investments in capacity building for data collection, analysis and research literacy.

To deliver impact, evidence must be generated and disseminated in a manner that supports 'real-world' applications. This will require attentiveness to the specific questions, outcomes and evidence outputs that are most salient to a range of decision makers, whether they be potential users, providers, procurers, policymakers, funders or developers of HIV prevention products. There is a need to engage these key stakeholders early in the research process to ensure that research informs specific policy questions and decisions of relevance.

Doing so will require community-centred research in populations and geographies that are currently under-represented. Target group-specific research is preferable; in its absence, it is important to include target groups in broader research efforts, for instance by including transgender or pregnant people in studies that target cis-gender women or the general population and ensuring sufficient data disaggregation. When collecting data with marginalised communities, engaging clinicians, researchers and trusted community advisors from these communities can be critical in improving trust. To close historical gaps in evidence on neglected groups and regions, investments may be needed to strengthen capacity in routine data collection, socio-behavioural research and health economics research in a broader range of LMIC settings.

4.1.4 Fostering an Active Network of Partners Across Sectors

Recommendation 4: A broader active network of partners across sectors is necessary to ensure high-quality health economics research can fill remaining gaps, including

greater synergies between funding streams, investment in shared frameworks and tools, alignment on methods, and mechanisms for coordination between sectors to collectively prioritise, resource and cohesively address gaps.

Stronger links and better communications across a network of partners in different sectors (e.g. academia, donor organisations, national governments and others) will be needed to strengthen future health economics research efforts. Expanded investment in costing studies across settings and service delivery models is needed. Important synergies across funding streams, disease areas and health economics exist [77] and could be utilised more efficiently to bolster data collection capacity and support understanding of integrated strategies. Routine data collection systems, particularly those linked to national surveillance systems, must be improved, and expanded to include relevant health economics data inputs, particularly the expansion of disaggregated data accounting for a range of user characteristics, so that equity can be properly evaluated.

Improved platforms for coordination and resource-sharing across donors, health economists and others working across linked programmatic areas will be needed to support this goal. Examples of platforms for cross-sector collaboration and resource-sharing are already in place across HIV and other disease areas (e.g. PEPFAR's Resource Alignment, the Access to COVID-19 [ACT] Accelerator) and could serve as models for such multi-stakeholder coordination. Donors or multilateral partners could play a convening role in the establishment of such platforms.

4.1.5 Enhanced Application of Evidence

Recommendation 5: Evidence must support 'real-world' applications through engagement with key stakeholders early in the research process; evidence should be presented in a manner that is useful for decision makers and calibrated to different stages of product development.

While this study identified research gaps, it also highlighted the need for greater attentiveness to how to best use existing evidence, even if limited, to inform decision making. Complexity in the methods and scope should not translate into overly technical key policy and advocacy messages. Evidence needs to be presented in a manner that is useful for decision makers. Further, cost-effectiveness data should be presented in ways that engage a number of actors facing different decisions within and beyond Ministries of Health, such as Ministries of Finance, donors, public-private partnerships and users.

Findings should also be presented to communities. Greater effort is needed to enhance research literacy and to present evidence in a way that can be understood by different types of stakeholders and interested parties. Health economics research in HIV prevention also needs to be contextualised within the global agenda of Universal Health Coverage and national health benefit package design processes. The majority of HIV funding in LMICs comes from national sources. As such, health economics evidence must be built with attentiveness to the data needs not only of donors, but of national governments facing hard decisions about their own resources, including those transitioning from donor support. Evidence on both cost effectiveness and affordability is needed to inform decision making, and to highlight budget impacts alongside economic costs and benefits.

To adequately inform decision making, it is also important to calibrate efforts to the stage of product development. Different types of evidence might be important at different stages of the development, introduction and scale-up continuum. Before a product is developed, threshold analyses can be helpful in assessing the maximum a product could cost to be cost effective (or conversely the minimum effectiveness it could have) to inform target product profiles. As products are closer to launch, budget impact, willingness-to-pay assessments and co-financing analyses may become more relevant. Further, greater differentiation between price and cost is needed in published analyses. While some products may not initially prove cost effective, policy levers (e.g. voluntary mechanisms to license or flexibilities under the Agreement on Trade-Related Aspects of Intellectual Property Rights [79]) could potentially be pulled to reduce prices and increase value for money; researchers should engage with this type of policy decision.

Greater clarity is needed on the appropriateness of different cost-effectiveness thresholds for different types of decisions. The limitations of cost-effectiveness thresholds, particularly in a context of declining incidence, should be acknowledged and outcome measures beyond cost effectiveness should be considered. Further, evidence should be interpreted within country contexts and the resources necessary to address the epidemic at current and subsequent stages.

Similarly, the limitations of incremental cost-effectiveness ratios (ICERs) need to be better explained and understood. Incremental cost-effectiveness ratios can change substantially between settings and over time due to variation in key inputs, such as price. Comparability between ICERs is therefore limited. Additionally, ICERs miss positive externalities of prevention outside the health sector, an issue of particular concern in HIV that has particular intersectoral spillover effects (e.g. retention of adolescent girls in school [80]). More cautious and flexible approaches to the interpretation of ICERs would better reflect uncertainty and 'real-world' impacts of prevention within health technology assessment processes.

4.2 Limitations

While this mixed-methods study was designed to systematically capture evidence, there are certain potential weaknesses to our approach. While three main health economics areas were targeted in the systematic reviews, other methodological approaches may have been excluded (e.g. behavioural experiments). To map recently completed, ongoing and future research, we contacted identified researchers with prior publications. However, we may not have captured researchers new to this area. Further, our survey response rate was low. Finally, while the stakeholder consultation was extremely rich in content, our analysis may have benefited from a longer session and greater opportunity to exchange ideas, as well as in-person interactions and a greater number of participants from some sectors, especially patient and advocacy groups.

5 Conclusions

Despite a large body of health economics evidence on non-surgical, biomedical HIV prevention technologies, important gaps in scope and methodology remain. Some key and vulnerable populations, settings, technologies and delivery modalities have not been fully researched. Further, a methodological emphasis on equity, heterogeneity and 'real world' complexity is largely missing, leading to suboptimal evidence informing product development and implementation policy. We propose a number of recommendations across five broad areas to ensure that high-quality research influences key decision-making junctures, facilitating the delivery of prevention products in a way that maximises impact.

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Declarations

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Conflict of interest MQ reports current employment at a healthcare consultancy (Evidera) but does not work in the HIV prevention area in this role. All other authors declare that they have no competing interests.

Ethics approval Ethical approval for this study was obtained from the Research Ethics Committee of the London School of Hygiene & Tropical Medicine.

Consent to participate Patients provided consent to participate in this study.

Consent for publication Not applicable.

Availability of data and material This study produced quantitative data from an online survey and qualitative data from a stakeholder meeting. These data are available upon request.

Author's contributions FTP, SM, GM, MG and STR conceived of the study and reviewed the methods. FB, PPI and RG carried out the literature reviews with support from MQ, MG, FTP and STR. STR carried out data collection for the survey and stakeholder meeting. STR, FTP and SM led the analysis, with feedback from all authors. STR drafted the manuscript with support from FTP and SM. All authors read and approved the final version of the manuscript.

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