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HIV IN A GLOBAL CONTEXT: IMPACT OF PREVENTION, TREATMENT AND PUBLIC HEALTH STRATEGIES ON CLINICAL AND EPIDEMIOLOGICAL OUTCOMES - SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: To assess the impact of the main prevention, treatment, and public health strategies related to HIV on clinical and epidemiological outcomes across different populations and global contexts. **Methods:**A systematic review with thematic meta-analyses was conducted, following the PRISMA 2020 recommendations. Searches were performed in MEDLINE/PubMed, Embase, Scopus, Web of Science, CENTRAL, and LILACS, as well as in clinical trial registries and reference lists of eligible studies, considering publications available up to 21 July 2026. Individual randomized controlled trials or cluster-randomized trials, prospective cohorts, and longitudinal population-based studies evaluating HIV-related prevention, treatment, or implementation strategies were included. Outcomes included incidence of infection, sexual and mother-to-child transmission, mortality, AIDS-related events, viral suppression, linkage to, and retention in, care. Quantitative syntheses were conducted separately by intervention and outcome, using random-effects models.**Results:**Forty independent studies were included, covering pre-exposure prophylaxis, voluntary medical male circumcision, treatment as prevention, prevention of mother-to-child transmission, early initiation of antiretroviral therapy, treatment regimens, prophylaxis for advanced disease, and community interventions. Oral PrEP reduced HIV acquisition, with a pooled relative risk of 0.42, although with high heterogeneity mainly associated with adherence. Male circumcision showed a pooled relative risk of 0.45, with no relevant heterogeneity. Injectable cabotegravir and semiannual lenacapavir had incidences lower than those observed with oral PrEP. Early initiation of antiretroviral therapy reduced severe events, tuberculosis, and mortality. Treatment as prevention substantially reduced sexual transmission, and no genetically linked transmissions were observed during approximately 3.063 couple-years of exposure under viral suppression. Combined therapy reduced mother-to-child transmission to below 2% in settings with high adherence. Community interventions showed heterogeneous results, dependents of linkage, retention, and viral suppression.**Conclusion:**The strategies currently available are capable of significantly reducing the incidence, transmission, morbidity, and mortality related to HIV. The greatest impact was observed when highly effective biomedical interventions were combined with early diagnosis, universal treatment, sustained adherence, and continuity of care. Reducing the global burden of HIV depends on the equitable expansion of access, strengthening health systems, and addressing the social and structural barriers that limit the effectiveness of interventions.

Keywords:HIV Infections; Pre-Exposure Prophylaxis; Highly Active Antiretroviral Therapy; Public Health.

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INTRODUCTION

Infection with the human immunodeficiency virus remains one of the main public health challenges worldwide, despite advances achieved in diagnosis, prevention, and treatment. The evolution of antiretroviral therapy transformed a condition previously associated with high mortality into a controllable chronic disease, enabling greater survival, immune recovery, and a significant reduction in the occurrence of opportunistic infections. However, the persistence of new infections, late diagnoses, mother-to-child transmission, failures in linkage to care, and inequalities in access to preventive technologies show that controlling HIV does not depend exclusively on the availability of medications, but also on the ability to incorporate them continuously, equitably, and adapted to different epidemiological contexts.

The global response to HIV has undergone a progressive paradigm shift. Initially focused on reducing risk behaviors and using condoms, preventive strategies began to incorporate biomedical interventions capable of directly modifying the likelihood of acquiring or transmitting the virus. Among these interventions, pre-exposure prophylaxis, voluntary medical male circumcision, prevention of mother-to-child transmission, and antiretroviral treatment used simultaneously stood out as resource therapeutic and preventive.

Pre-exposure prophylaxis represented one of the main advances in preventing HIV in people initially HIV-negative. Early trials showed that oral use of tenofovir, alone or combined with emtricitabine, reduced acquisition of the virus among men who have sex with men, heterosexual serodiscordant couples, heterosexual serodiscordant individuals, heterosexual men and women, and people who used injectable drugs (1-4) . Subsequently, on-demand regimens and strategies pragmatic of immediate availability confirmed that PrEP could provide high protection when used appropriately (5,6) .

The effectiveness of oral PrEP, however, proved to be strongly dependent on adherence. While studies with high pharmacological exposure demonstrated significant reductions in incidence, the

FEM-PrEP trial did not identify a significant benefit among African women given the low objective use of the medication (17). This discrepancy showed that the pharmacological efficacy observed under ideal conditions does not automatically translate into population-level effectiveness. Barriers related to stigma, individual perception of risk, the need for daily use, negotiation with partners, access to services, and continuity of follow-up can limit the impact of the intervention.

Comparing different oral formulations showed that FTC/TAF had efficacy not inferior to the combination of FTC/TDF in certain populations, with differences in renal, bone, and metabolic profiles (7). More recently, long-duration modalities have again changed the preventive landscape. Periodically administered injectable cabotegravir performed better than daily oral PrEP among cisgender men, transgender women, and cisgender women exposed to the risk of infection (8,9). Similarly, twice-yearly subcutaneous lenacapavir produced extremely low incidence among women, men, and people of gender diversity, demonstrating the potential of strategies that reduce dosing frequency and reliance on daily behavior (10, 11).

Other preventive technologies also helped expand the available options. The tenofovir vaginal gel provided partial protection among women, with greater effectiveness in those who demonstrated higher adherence (12). The RV144 vaccination regimen produced a modest reduction in HIV acquisition, constituting initial evidence that preventive immunization could alter the risk of infection, although the observed protection was limited and insufficient for use alone as a control strategy (13).

Voluntary medical male circumcision demonstrated benefit

consistent with reducing heterosexual acquisition of HIV in men who were initially HIV-negative. Trials conducted in South Africa, Kenya, and Uganda identified similar effects, strengthening its

its incorporation into combination prevention programs in regions with high heterosexual transmission and low circumcision prevalence (14- 16). Despite the benefit, protection was partial and did not eliminate the need for association with

condoms, testing, PrEP, and other preventive measures.

Alongside advances in preventing acquisition, antiretroviral therapy has been consolidated as a central element to prevent sexual transmission. O HPTN 052 showed that the early start of treatment substantially reduced as transmissions

genetically linked in serodifferent couples (18). Subsequently, the PARTNER and Opposites Attract cohorts did not identified transmissions

linked during periods of sustained viral suppression, even in the presence of condomless sex (19-21). These findings supported the principle that an undetectable viral load prevents sexual transmission, giving treatment value that is simultaneously individual, relational, and population-level.

Preventing mother-to-child transmission is another example of a transformation produced by antiretrovirals. The use of zidovudine during pregnancy, childbirth, and the neonatal period substantially reduced transmission compared with placebo (22). The later development of combined regimens during pregnancy and breastfeeding made it possible to achieve progressively lower rates of childhood infection, as demonstrated in the Mma Bana, Kesho Bora, and PROMISE studies (23-25). Although vertical transmission can be reduced to very low levels, its persistence in certain regions reveals failures in prenatal diagnosis, timely initiation of treatment, maternal viral suppression, and retention of the mother–child dyad in care.

The anticipation of treatment also produced direct clinical benefits for people living with HIV. The START, TEMPRANO trials, and the study conducted in Haiti showed that starting therapy early reduced serious events related to AIDS, non–AIDS-related diseases, tuberculosis, and mortality, including among participants with counts relatively preserved of CD4 lymphocytes (26-28). These results contributed to the replacement of deferred-treatment-based strategies with recommendations to start treatment after diagnosis.

The choice of antiretroviral regimens has also evolved. Studies such as ADVANCE and NAMSAL demonstrated high virological effectiveness of regim-

ens containing dolutegravir in initial treatment, although they identified a greater weight gain in certain groups (29,30). Among people with failure on the first regimen, the DAWNING and NADIA trials showed that regimens with high genetic barrier drugs could maintain high viral suppression and expand second-line options across different care settings (31,32). For individuals with advanced disease, the association between antiretroviral therapy and expanded prophylaxis against opportunistic infections reduced mortality, tuberculosis, cryptococcosis and hospitalizations, demonstrating that the start of therapy must be accompanied by additional interventions when there is severe immunosuppression (33) .

Despite the high efficacy demonstrated at the individual level, the population impact of interventions depends on how the prevention and care cascade functions. Community trials that assessed universal testing, expanded treatment, and combined strategies showed heterogeneous results. HPTN 071 PopART and the Botswana Combination Prevention Project demonstrated a reduction in incidence in certain scenarios, while SEARCH and ANRS 12249 TasP no identified significant differences between the intervention and control groups (34-37) . These divergences indicated that testing and treatment alone produce community-level reduction in transmission only when accompanied by effective linkage, timely initiation, retention, adherence, and viral suppression.

Strategies aimed at reducing care barriers have also proved relevant. Rapid initiation or same-day antiretroviral therapy increased the proportion of participants who started treatment, remained in care, and achieved viral suppression in the RapIT studies and in the trial conducted in Haiti (38,39). At the population level, higher community coverage of antiretroviral therapy was associated with a lower individual risk of acquiring HIV in a high-prevalence area in South Africa, providing additional evidence of the collective effect of therapeutic expansion (40).

The diversity of the findings shows that controlling HIV requires a combination of preventive technologies, universal treatment, clinical follow-up, virological monitoring, and structural interventions. Highly effective strategies may have re-

duced impact when stigma, gender inequality, criminalization, instability in medication supply, low testing coverage, and difficulties accessing services persist. Similarly, community interventions may not produce the expected effects when successive losses occur between diagnosis, linkage, treatment initiation, and viral suppression.

Although different interventions have been widely studied, the evidence is distributed across populations, geographic contexts, preventive modalities, and distinct outcomes. Integrating these findings from a global perspective is necessary to understand which strategies offer the most consistent benefits, which depend strongly on adherence, and which face greater limitations in implementation.

Against this backdrop, this systematic review with thematic meta-analyses aimed to assess the impact of the main HIV prevention, treatment, and public health strategies on clinical and epidemiological outcomes. Incidence of infection, sexual and mother-to-child transmission, mortality, events related to AIDS, viral suppression, linkage to care, and the effectiveness of community interventions were examined, seeking to identify the magnitude of benefits, the sources of heterogeneity, and the implications for global epidemic control policies.

METHODOLOGY

A systematic review with thematic meta-analyses was carried out to assess the impact of prevention, treatment, and public health strategies related to HIV on clinical and epidemiological outcomes. The conduct and reporting of the review followed the recommendations of the *Preferred Reporting Items for Systematic Reviews and MetaAnalyses*- PRISMA 2020 - and the methodological principles applicable to systematic reviews of interventions. Given the broad thematic scope and clinical heterogeneity across the strategies evaluated, the studies were brought together in a comprehensive systematic review, but the quantitative syntheses were planned and conducted separately according to the type of intervention, the population studied, the comparator, and the outcome analyzed. As a result, a

single combined estimate was not calculated indiscriminately involving all prevention, treatment, and public health strategies.

The research question was structured according to the PICOS model. The population of interest included HIV-negative people at risk of acquiring the virus, people living with HIV, serodifferent couples, pregnant women living with HIV and their children, men eligible for voluntary medical male circumcision, and populations followed in community interventions or public health programs. The interventions evaluated included oral, topical, injectable, or semiannual pre-exposure prophylaxis, preventive vaccination, voluntary medical male circumcision, antiretroviral treatment as prevention, early initiation of antiretroviral therapy, prevention of mother-to-child transmission, first- and second-line antiretroviral regimens, expanded prophylaxis for people with advanced disease, universal testing, rapid initiation or same-day initiation of antiretroviral therapy, linkage to care, and combined community interventions. The comparators included placebo, absence of intervention, usual care, deferred initiation of antiretroviral therapy, conventional prophylaxis, alternative antiretroviral regimens, active oral PrEP, and estimated baseline incidence. The main outcomes considered were incidence of HIV infection, genetically linked sexual transmission, mother-to-child transmission, all-cause mortality, AIDS-related events, viral suppression, initiation of antiretroviral therapy, retention in care, occurrence of opportunistic infections, and serious adverse events.

The bibliographic search was conducted in the MEDLINE/PubMed, Embase, Scopus, Web of Science Core Collection, Cochrane Central Register of Controlled Trials – CENTRAL – and Latin American and Caribbean Health Sciences Literature – LILACS/BVS databases. Clinical trial registers were also consulted, including ClinicalTrials.gov and the World Health Organization's international clinical trial registry platform. The reference lists of eligible studies were manually reviewed in order to identify additional potentially relevant publications. The search period covered the initial indexing of each database up to July 21, 2026. No initial restrictions were applied regarding country, geographic region, or language of publication.

The search strategy combined controlled vocabulary, including MeSH descriptors, Emtree, and DeCS, with related free-text terms for HIV, preventive and therapeutic interventions, and epidemiological study designs of interest. Corresponding terms were used for "HIV", "human immunodeficiency virus", "pre-exposure prophylaxis", "PrEP", "antiretroviral therapy", "treatment as prevention", "viral suppression", "universal testing", "test and treat", "same-day treatment", "male circumcision", "vaccine", "microbicide", "mother-to-child transmission", "vertical transmission", and "community intervention". These terms were combined with Boolean operators and methodological filters related to randomized clinical trials, trials by clusters, prospective studies, cohorts, and population-based investigations. The syntax was adapted to the specific characteristics of each database, while maintaining the same conceptual blocks.

Studies were included with human participants living with HIV or presenting a risk of acquiring infection, provided they assessed a clinical, preventive, therapeutic, or public health strategy related to HIV and reported at least one relevant clinical, virological, or epidemiological outcome. Individual randomized clinical trials, cluster randomized trials, prospective cohort studies, and longitudinal population studies were eligible. The presence of an explicit comparator was also required or, in the case of prospective studies on viral suppression and non-transmissibility, measurement adequate measurement of exposure time and genetically linked transmissions. The studies should provide sufficient quantitative data for extraction or calculation of an effect measure.

Narrative reviews, systematic reviews, meta-analyses, editorials, letters, comments, protocols without results, case reports, case series, studies exclusively cross-cutting, qualitative investigations, pre-clinical research, studies *in vitro*, animal experiments, and mathematical models without empirical data from human participants. Studies without relevant clinical, virological, or epidemiological outcomes were also excluded, as were publications with insufficient data for extraction and secondary reports that reproduced participants and outcomes already counted in another publication. When the same study presented interim

and final analyses, the publication with the most complete follow-up for the corresponding outcome was prioritized.

The identified records were organized in a bibliographic manager and subjected to automatic and manual duplicate removal. The selection took place in two stages. Initially, titles and abstracts were assessed. Next, the full texts of potentially eligible records were reviewed according to the criteria previously established. The reasons for exclusion at the full-text screening stage were recorded. The identification, screening, eligibility, and inclusion process was structured for presentation in a flow diagram according to the PRISMA 2020 model.

The primary study, and not each published article, was considered the unit of analysis. Publications related to the same trial were linked using the study acronym, registration number, participating centers, sample characteristics, and recruitment period. When were interim and final publications referring to the same participants identified, the publication with the longest follow-up time was used in the main analysis, while complementary information was retrieved from secondary reports without any new counting of the participants. In the case of HPTN 052, the final publication was considered for the long-term analysis of sexual transmission of HIV.

Data extraction was carried out using a standardized form. Information was collected regarding the author, year of publication, study acronym, country, geographical region, methodological design, number of centers or clusters, eligibility criteria, demographic and clinical characteristics of participants, sample size, intervention, dose, frequency, duration, comparator, follow-up period, adherence, losses to follow-up, interruptions, definition of outcomes, number of events, denominators, person-years or couple-years, effect measures, confidence intervals, adverse adverse events, funding, conflicts of interest, and methodological limitations. In randomized trials, an intention-to-treat analysis was prioritized. In observational studies, estimates with the greatest control for clinically relevant confounding factors were extracted preferentially.

The primary outcomes were incidence of HIV infection, genetically linked sexual transmission, mother-to-child transmission, all-cause mortality, serious events related to AIDS, and viral suppression. Secondary outcomes included initiation of antiretroviral therapy, linkage to and retention in care, tuberculosis and other opportunistic infections, hospitalization, serious adverse events, discontinuation of the intervention, prematurity, low birth weight, renal, bone, or metabolic changes, and resistance to antiretrovirals.

The risk of bias in individual randomized clinical trials was assessed using the RoB 2 tool, considering the randomization process, deviations from the intended interventions, missing data, outcome measurement, and the selection of reported results. In cluster randomized trials, we also considered the timing of identification and recruitment of participants, the baseline imbalance between clusters, loss of clusters, and the possibility of contamination between communities. Observational studies were assessed using the ROBINS-I tool, considering confounding, selection of participants, classification of interventions or exposures, deviations from the intended exposure, missing data, outcome measurement, and the selection of reported results. Each study was classified according to the overall risk-of-bias judgment applicable to the respective instrument.

Meta-analyses were organized according to groups clinically homogeneous. Separate syntheses were conducted for oral PrEP, injectable or semiannual PrEP, voluntary medical male circumcision, treatment as prevention, prevention of mother-to-child transmission, early initiation of antiretroviral therapy, virological effectiveness of treatment regimens, rapid initiation of therapy, and community interventions for testing and treatment. Vaccine studies, topical microbicides, and expanded prophylaxis for advanced disease were analyzed separately when there was not a sufficient number of clinically comparable clinical studies.

For dichotomous outcomes with similar follow-up time, relative risks with 95% confidence intervals were used. For events expressed as a function of exposure time, incidence rate ratios were emp-

loyed. When studies presented survival analyses, the *hazard ratios* and their respective confidence intervals were used as the primary measures. Adjusted estimates were prioritized in cluster trials and in observational studies. Different effect measures were not directly combined without a methodologically justified transformation.

Quantitative syntheses were performed using random-effects models, considering the expected variability among populations, geographic regions, interventions, adherence levels, and implementation contexts. Statistical heterogeneity was assessed using Cochran's Q test, the I^2 statistic, and the variance between studies represented by τ^2. High values of I^2 were interpreted together with the magnitude and direction of the effects, confidence intervals, and the clinical and methodological differences between studies.

In multi-arm studies, the shared comparator group was handled to avoid double counting. When appropriate, similar arms were combined; alternatively, the comparator group denominator was divided proportionally across comparisons. In factorial trials, adjusted estimates for the main effects were prioritized. Studies with zero events in one arm were analyzed using appropriate methods for rare events. In cohorts on viral suppression and nontransmissibility, in which no transmissions linked to the intervention were observed, rates were calculated per person-year or per couple-year with exact confidence intervals, without the use of a conventional relative risk in the absence of an unsuppressed comparator group.

Subgroup analyses were planned according to PrEP modality, route of administration, population, sex, geographic region, adherence, methodological design, type of comparator, duration of follow-up, and level of coverage of the interventions. Sensitivity analyses considered excluding studies with high risk of bias, observational studies, trials stopped early, publications with reduced pharmacological adherence, and investigations that used estimated baseline incidence instead of a contemporaneous randomized comparator. Where feasible, fixed- and random-effects models were also compared.

The assessment of publication bias was planned only for meta-analyses with at least ten clinically comparable studies. In these cases, funnel plots and asymmetry tests appropriate to the effect size were used. The interpretation considered that asymmetries could result from heterogeneity, differences in the size of the studies, rare events, or methodological characteristics, and not exclusively from publication bias.

The certainty of the body of evidence was assessed using the GRADE system for each clinically relevant outcome. Risk of bias, inconsistency, indirect evidence, imprecision, and publication bias. Evidence from randomized trials started with a rating of high certainty and was downgraded when important limitations were identified. Observational evidence started with a lower certainty rating, which could be upgraded when they demonstrated a large magnitude of effect, dose-response relationship, or when plausible confounding factors would tend to reduce the observed effect.

The statistical analyses were conducted in R, using appropriate packages for meta-analysis and synthesis of intervention studies. Two-tailed tests were adopted, a significance level of 5%, and 95% confidence intervals. As only exclusively data previously published and available in scientific sources, no submission to a research ethics committee was required.

RESULTS

The final synthesis comprised 40 independent studies published between 1994 and 2025, covering biomedical, therapeutic, and population-level strategies related to controlling HIV infection. We identified 32 individual randomized controlled trials, four cluster randomized trials, and four prospective or population-based observational studies. The investigations were conducted in the Americas, Europe, Africa, Asia, and Oceania, including heterosexual populations, men who have sex with men, cisgender women, transgender and gender-diverse people, people who used injectable drugs, serodiscordant couples, pregnant individuals living with HIV, children exposed to the virus, and communities with a high epidemiological burden. Sample sizes ranged

from a few hundred participants or couples to community interventions that reached hundreds of thousands of residents.

Among the 40 studies, 12 assessed different pre-exposure prophylaxis modalities; one investigated a vaginal microbicide; one evaluated preventive vaccination; three examined voluntary medical male circumcision; four investigated treatment as prevention and nontransmissibility during viral suppression; four assessed prevention of mother-to-child transmission; three compared early versus deferred initiation of antiretroviral therapy; four analyzed first- or second-line antiretroviral regimens; one evaluated expanded prophylaxis for advanced disease; and seven investigated community strategies, universal testing, linkage to care, or rapid initiation of treatment.

Oral pre-exposure prophylaxis showed an overall preventive benefit, although the magnitude of the effect varied substantially depending on the population, the regimen used, and, above all, adherence. In the iPrEx, Partners PrEP, TDF2, Bangkok Tenofovir Study, IPERGAY, and PROUD trials, the relative reduction in HIV acquisition ranged approximately between 44% and 86% (1-6). In contrast, FEM-PrEP did not demonstrate significant benefit, with 33 infections in the FTC/TDF group and 35 in the placebo group—a result associated with low objective pharmacological exposure and insufficient adherence (17). Combining the seven trials that compared oral PrEP with placebo or delayed initiation, after the meeting of the active arms of Partners PrEP to avoid double counting of the control group, produced a pooled relative risk of 0.42, with a 95% confidence interval between 0.27 and 0.65. This result corresponded to an approximate 58% relative reduction in HIV acquisition. Heterogeneity was high, with I 2 of 70.4% and p=0.002 in the Q test, reflecting important differences in adherence, population, administration regimen, and epidemiological context.

The DISCOVER trial demonstrated that FTC/TAF was not inferior to FTC/TDF, with seven infections in the FTC/TAF group and 15 in the FTC/TDF group, as well as a more favorable profile in renal and bone markers, although accompanied by greater weight gain and lipid changes (7). Since both groups received active prophylaxis, this study was not included in the meta-analysis of oral PrEP versus placebo or no intervention.

Injectable long-acting modalities produced the largest effect magnitudes among PrEP strategies. In HPTN 083, 13 infections were recorded among participants who received cabotegravir and 39 among those who used FTC/TDF, corresponding to an approximate 66% reduction in the risk of acquisition (8). In HPTN 084, four infections occurred in the cabotegravir group and 36 in the FTC/TDF group, with a reduction close to 88% (9). In PURPOSE 1, no infection was identified among women who received semestral lenacapavir, while 39 infections occurred in the FTC/TAF group and 16 in the FTC/TDF group (10). In PURPOSE 2, two infections were observed among participants treated with lenacapavir and nine among those who received FTC/TDF, with incidence substantially lower than the estimated baseline incidence (11). Taken together, these results indicated the superiority of long-acting modalities over daily oral PrEP in the contexts studied, although differences in adherence among the comparators and the use of baseline incidence in part of the analyses limited the possibility of a single pooled estimate.

The vaginal gel of tenofovir evaluated in CAPRISA 004 reduced the incidence of HIV by approximately 39%, with higher protection among women with greater adherence to the product (12). The RV144 vaccine trial showed preventive efficacy of 31.2% in the modified intention-to-treat analysis, with no relevant effect on viral load or CD4 lymphocyte counts among participants who acquired the infection (13). Because of differences in mechanism, administration, and population, these studies were analyzed individually.

The three randomized trials of voluntary medical male circumcision demonstrated consistent results. ANRS 1265 identified an approximate 60% reduction in heterosexual acquisition of HIV, while the Kisumu and Rakai trials observed reductions close to 53% and 51%, respectively (14-16). A meta-analysis of the three studies produced a pooled relative risk of 0.45, with a 95% confidence interval between 0.33 and 0.61, equivalent to a relative reduction of approximately 55%. No relevant statistical heterogeneity was identified, with I 2 of 0% and p=0.854. Protection was directed mainly toward heterosexual acquisition of HIV

by men who were initially seronegative and did not represent complete protection or a substitute for other preventive measures.

Antiretroviral treatment as prevention showed an effect of high magnitude. In the final follow-up of HPTN 052, three genetically linked transmissions were identified in the early-therapy initiation group and 43 in the initially deferred group, corresponding to an approximately 93% reduction in sexual transmission (18). The transmissions that occurred in the early-treatment group were associated with the period before complete viral suppression or virologic failure.

The PARTNER 1, PARTNER 2, and Opposites Attract studies did not identify genetically linked transmission during periods of viral load below 200 copies/mL, despite the occurrence of sex without a condom (19-21). Considering the strictly eligible periods, without PrEP use by the HIVnegative partner and with documented viral suppression, the three studies accumulated approximately 3,063 couple-years with no linked transmission. The observed rate was zero transmissions per 100 couple-years, with an upper limit of the estimated 95% confidence interval of 0.12 per 100 couple-years. These results supported the conclusion that the risk of sexual transmission during stable viral suppression was effectively zero under the conditions assessed.

prevention strategies for transmission mother-to-child

they showed progressive evolution from isolated zidovudine to combined antiretroviral therapy. In PACTG 076, transmission occurred in 8.3% of children exposed to zidovudine and in 25.5% of children in the placebo group, representing a relative reduction of 67.5%

(22). In the Mma Bana study, the combination regimens during pregnancy and breastfeeding produced an overall transmission rate close to 1.1%, with no substantial difference between the active regimens, although the regimen containing lopinavir/ritonavir was associated with a higher frequency of preterm births (23). In Kesho Bora, transmission at 12 months was approximately 5.4% with triple therapy and 9.5% with the conventional prophylaxis used during the study period (24). In PROMISE, perinatal transmission was approximately 0.5% in the groups that received combination therapy and 1.8% in the group assigned to the

zidovudine-based prophylactic regimen, although some regimens showed a higher frequency of maternal, gestational, or neonatal adverse events (25). The heterogeneity of regimens, follow-up periods, and breastfeeding practices prevented a single estimate for the entire set.

The early initiation of antiretroviral therapy reduced serious clinical events and mortality. In START, 42 primary events occurred among participants who started treatment immediately and 96 among those assigned to deferred initiation, with a hazard ratio of 0.43 and an approximate 57% reduction in the composite outcome of serious events related or unrelated to AIDS and death (26). In TEMPRANO, early initiation produced an adjusted hazard ratio of approximately 0.56 for the composite outcome, while isoniazid prophylaxis also showed an independent benefit (27). In the trial conducted in Haiti, there were six deaths among 408 participants in the early initiation group and 23 among 408 participants in the standard group, as well as a lower incidence of tuberculosis in the group treated immediately (28). Despite the consistency in the direction of the effects, the studies were not combined into a single estimate due to differences in the composite outcomes, CD4 thresholds, and follow-up times.

In trials of antiretroviral regimens, regimens containing dolutegravir showed high virologic effectiveness. In ADVANCE, the proportion of participants with viral load below 50 copies/mL at week 48 was approximately 84% with dolutegravir and TAF, 85% with dolutegravir and TDF, and 79% with efavirenz and TDF, confirming the non-inferiority of the two dolutegravir-containing regimens (29) . In NAMSAL, viral suppression occurred in approximately 74.5% in the dolutegravir group and 69.0% in the low-dose efavirenz group, also meeting the non-inferiority criterion (30) . Both studies identified greater weight gain associated with dolutegravir, especially among women and among participants who used TAF.

Among people with failure of initial treatment, DAWNING demonstrated viral suppression in approximately 84% of participants who received dolutegravir and in 70% of those who received lopinavir/ritonavir, confirming the superiority of the dolutegravir-based regimen (31) . In NADIA, viral suppression below 400 copies/mL occurred in

approximately 90.2% with dolutegravir and 91.7% with darunavir/ritonavir, while maintaining tenofovir produced a result that was non-inferior to switching to zidovudine (32) . These studies indicated high effectiveness of regimens with drugs with a high genetic barrier, although the different viral suppression thresholds limited the direct combination of the estimates.

In the REALITY study, expanded prophylaxis for participants with CD4 counts below 100 cells/mm 3 reduced mortality over 24 weeks from approximately 12.2% to 8.9%, with a hazard ratio of 0.73. Reductions in tuberculosis, cryptococcosis, candidiasis, hospitalizations, and other serious events were also observed (33). Since the intervention involved multiple medications simultaneously, it was not possible to attribute the effect to an isolated component.

The results of community interventions were more heterogeneous than those observed in individual biomedical strategies. In HPTN 071 PopART, the arm that received the community package with treatment according to national guidelines showed an approximate 30% reduction in incidence compared with standard of care, while the theoretically more intensive arm, with universal treatment from the outset, did not show a statistically significant reduction (34) . In SEARCH, the cumulative incidence cumulative was approximately 0,77% in in intervention communities and 0.81% in the control communities, with no significant difference between the groups, although progress was observed in viral suppression and other care indicators (35) .

No Botswana Combination Prevention Project, the incidence was approximately 0.59 per 100 person-years in the intervention communities and 0.92 in the control communities, corresponding to an adjusted reduction of around 30% (36) . In ANRS 12249 TasP, the incidences were approximately 2.11 and 2.27 per 100 person-years, with an adjusted hazard ratio of around 1.01, showing no reduction in community incidence. The low linkage to services and the smaller-than-expected difference between the groups were considered relevant factors for the lack of effect (37) .

Rapid start or same-day initiation strategies improved steps in the care cascade. In RapIT, approximately 97% of

participants in the rapid-start group started therapy, compared with 72% in standard care. The combined outcome of treatment initiation and viral suppression was achieved by 64% and 51%, respectively, with an approximate relative risk of 1.26 (38) . In the study conducted in Haiti, same-day initiation increased 12-month retention from approximately 72% to 80%, increased the proportion of participants retained with viral load below 50 copies/mL from 44% to 53%, and reduced mortality from about 6% to 3% (39) .

A population cohort in KwaZulu-Natal demonstrated an association between greater community coverage of antiretroviral therapy and a lower individual risk of acquiring HIV. Participants living in areas where 30% to 40% of people living with HIV were receiving treatment had an approximately 38% lower risk of acquiring the infection than those living in areas with coverage below 10%, with an adjusted hazard ratio of around 0.62 (40). Since this was an observational study with ecological exposure, the result was analyzed separately from randomized community trials.

Table 1. Summary of the main intervention groups and outcomes

Intervention Group	Studies	Predominant design	Primary outcome
Oral PrEP	1-7,17	Randomized trials	Pooled RR of 0.42 for PrEP versus placebo or delayed initiation; high heterogeneity mainly associated with adherence
Injectable or semiannual PrEP	8-11	Phase 3 randomized trials	Cabotegravir and lenacapavir substantially reduced incidence compared with oral PrEP or baseline incidence
Microbicide and vaccine	12-13	Randomized trials	39% reductions with tenofovir gel and 31.2% with the RV144 vaccine regimen
Male circumcision	14-16	Randomized trials	Pooled RR of 0.45; approximately 55% reduction; I^2=0%

Treatment as viral prevention and suppression	18-21	Randomized trial and cohorts	93% reduction in HPTN 052 and no linked transmissions in 3.063 couple-years under suppression
Prevention of vertical transmission	22-25	Randomized trials	Progressive reduction in transmission, reaching rates below 2% with combination therapy
Early initiation of ART	26-28	Randomized trials	Reduction of severe events, mortality, and tuberculosis
Antiretroviral regimens	29-32	Non-inferiority or superiority trials	High viral suppression with dolutegravir; greater weight gain in some groups
Prophylaxis for advanced disease	33	Randomized trial	Reduction in mortality and opportunistic infections
Community interventions and rapid initiation	34-40	Cluster trials, pragmatic trials, and cohort studies	Heterogeneous results for incidence; more consistent benefits in linkage to care, ART initiation, and viral suppression

The methodological assessment indicated that objective laboratory outcomes, such as HIV diagnosis and viral suppression, reduced the risk of measurement bias in most trials. The main limitations were related to insufficient adherence, especially in oral PrEP studies; lack of blinding in pragmatic and surgical trials; early discontinuation of some studies due to benefit; use of active comparators; losses to follow-up; contamination between communities; modifications of national guidelines during the trials by cohorts; and residual confounding in observational studies. In long-duration trials, the structural difference between a professional-administered intervention and an adherence-dependent oral comparator was also considered in interpreting the observed superiority.

Together, the certainty of the evidence was higher for the efficacy of PrEP

when there was adequate pharmacological exposure, for male circumcision in heterosexual acquisition by men, for the early initiation of antiretroviral therapy, and for treatment as prevention. Certainty was considered moderate for the absence of sexual transmission during viral suppression, due to the observational design of the main cohorts, despite the large amount of exposure time without transmission linked. Community interventions showed greater inconsistency and dependence on the implementation context, with overall certainty lower than that observed in individual biomedical interventions.

DISCUSSION

The results of this systematic review demonstrated that global HIV control depends on the integration of highly effective biomedical interventions, early and continuous access to antiretroviral therapy, combination prevention strategies, and the capacity of health systems to diagnose, link to care, and retain people in treatment. The synthesis of the 40 studies revealed consistent benefits for pre-exposure prophylaxis, voluntary medical male circumcision, early initiation of antiretroviral therapy, treatment as prevention, and prevention of mother-to-child transmission. However, the magnitude of the effects varied according to adherence, population, mode of delivery, program coverage, and the effectiveness of implementation in real-world settings.

Oral pre-exposure prophylaxis significantly reduced HIV acquisition, with a pooled relative risk of 0.42 in studies compared with placebo or delayed initiation, corresponding to an approximate relative risk reduction of 58%. The high heterogeneity observed in this synthesis did not appear to stem from fundamental pharmacological inconsistency, but mainly from differences in adherence. Trials such as Partners PrEP, IPERGAY, and PROUD showed high efficacy, while FEM-PrEP did not demonstrate significant protection due to low objective exposure to the medications (2,5,6, 17). This contrast reinforced that the biological efficacy of PrEP and its population-level effectiveness are not equivalent. Protection depends on the availability of the drug in the target tissues during the period of exposure to HIV, so isolated

prescribing does not guarantee benefit when there are social, behavioral, or structural barriers to continued use.

The results from iPrEx, TDF2, and the Bangkok Tenofovir Study also showed that oral PrEP can be effective in populations
epidemiologically distinct, including men who have sex with men, heterosexual populations, and people who use injectable drugs (1,3,4) . This diversity expanded the external validity of the strategy, although the magnitude of protection varied across the studies. The on-demand PrEP evaluated in IPERGAY showed high efficacy among men with frequent sexual exposures, but its extrapolation to other populations should consider differences in pharmacokinetics, frequency of exposures, and the possibility of using the event-related dosing schedule correctly (5) .

DISCOVER confirmed that FTC/TAF was not inferior to FTC/TDF for preventing HIV among cisgender men and transgender women who have sex with men, with a more favorable profile in renal and bone markers (7) . However, the higher incidence of weight gain and metabolic changes associated with the TAF regimen indicated that choosing the preventive regimen should consider not only antiviral efficacy, but also comorbidities, renal risk, bone health, metabolic profile, and individual preferences. The absence of cisgender women in the trial also limited the generalizability of this formulation to all populations eligible for PrEP.

Long-acting strategies represented one of the most significant advances identified. Injectable cabotegravir outperformed daily oral PrEP in the HPTN 083 and HPTN 084 studies, while the semi-annual lenacapavir showed extremely low incidence in PURPOSE 2 and no infections in the main arm of PURPOSE 1 (8-11). These results suggested that reducing the frequency of administration could overcome some limitations related to daily adherence, medication fatigue, stigma associated with pill use, and difficulty with private storage. However, the observed superiority should not be attributed exclusively to greater pharmacological potency. The comparison between an intervention administered periodically by professionals and a behavior-

dependent oral regimen incorporates a structural difference in adherence.

The implementation of long-acting PrEP also presents challenges. Reactions at the site of application, the need for infrastructure for administration, periodic attendance at services, timely diagnosis of incident infections, and the risk of resistance during the prolonged decline phase of drug concentrations are relevant aspects. In addition, technologies that are more complex and costly may widen inequalities if they are incorporated only into systems with greater financial capacity. The high efficacy observed in the trials will only produce impact have a global epidemiological effect if it is accompanied by equitable access, stable supply chains, regular testing, and strategies to reach populations historically underserved by services.

The vaginal gel of tenofovir showed moderate, adhesion-dependent protection, while the RVl44 vaccination regimen produced limited efficacy, although it provided evidence that a vaccine could partially reduce the acquisition of HIV (l2, l3). These findings showed that interventions with intermediate effectiveness can contribute to combination prevention, but are unlikely to be sufficient as standalone strategies. The absence of a vaccine product with high and durable protection maintains the need to integrate pharmacological methods, condoms, testing, and treatment of sexually transmitted infections and interventions behavioral and structural.

Voluntary medical male circumcision showed one of the most consistent results of the review. The three African trials demonstrated similar reductions in heterosexual acquisition of HIV in men, with a pooled relative risk of 0.45 and no relevant statistical heterogeneity (l4-l6). This consistency strengthened the evidence of benefit in regions with high incidence of heterosexual transmission and low circumcision prevalence. However, protection was partial and directed mainly toward acquisition in men who were initially HIV-negative. The intervention does not replace condoms, PrEP, testing, or antiretroviral treatment and should be offered voluntarily, safely, and with counseling to avoid the mistaken perception of full protection.

Treatment as prevention showed a particularly robust effect. HPTN 052 demonstrated a reduction of approximately 93% in genetically linked transmissions with early initiation of antiretroviral therapy, and the few identified transmissions occurred before complete viral suppression or in situations of virological failure (18) . The PARTNER 1, PARTNER 2, and Opposites Attract cohorts accumulated thousands of couple-years and tens of thousands of condomless sexual acts without registering genetically linked transmission during stable viral suppression (19-21) . These results provided consistent support for the principle that people with persistently undetectable viral load do not transmit HIV through sexual transmission.

The importance of the concept of undetectable equals untransmittable goes beyond biomedical prevention. Proper communication of this evidence can reduce stigma, fear, guilt, and discrimination, and also support testing, adherence, and treatment continuity. However, its application requires regular access to viral load testing, sustained adherence, continuous availability of medications, and rapid management of virological failures. In settings where laboratory monitoring is irregular or where there are frequent interruptions in the supply of medications, simply disseminating the message without adequate support from care services can generate clinical uncertainty.

The prevention of mother-to-child transmission showed a remarkable historical evolution. PACTG 076 demonstrated a significant reduction in transmission with zidovudine, establishing one of the first pieces of evidence that antiretroviral interventions could change the epidemiological course of HIV (22). Later, Mma Bana, Kesho Bora, and PROMISE showed that combined therapy during pregnancy and breastfeeding could reduce transmission to levels close to or below 2% in contexts of high adherence and appropriate follow-up (23-25). These results supported the expansion of universal treatment for pregnant women living with HIV.

Despite these advances, studies also showed that maternal and neonatal safety must be considered when choosing the regimen. Prematurity, low birth weight, toxicity, and metabolic or hematologic differences varied among the regimens evaluated. Vertical prevention does not depend only on prescribing antiretrovira-

ls, but also on early diagnosis during pregnancy, timely initiation of treatment, viral suppression at delivery, follow-up during breastfeeding, neonatal prophylaxis, and retention of the mother and child in care. The persistence of vertical transmission in certain settings likely reflects failures in coverage and continuity of care, rather than the absence of effectiveness of available interventions.

The START, TEMPRANO, and the study conducted in Haiti showed that delaying antiretroviral therapy exposed participants to a higher risk of events related to AIDS, non-AIDS conditions, tuberculosis, and death (26-28). The consistency of these findings confirmed that the benefits of treatment go beyond immune recovery in people with advanced disease. Early viral suppression reduces persistent inflammation, infectious complications and transmission, justifying the initiation of therapy regardless of CD4 lymphocyte count.

The ADVANCE, NAMSAL, DAWNING, and NADIA studies showed high effectiveness of regimens containing dolutegravir both as initial treatment and after virologic failure (29-32). The main genetic barrier to resistance, rapid viral suppression, and good tolerability favored these regimens. However, the weight gain observed, especially among women and participants exposed to TAF, indicated the need for metabolic monitoring. It is still not possible to interpret all weight gain as toxicity, since some may represent weight recovery after starting treatment. However, the occurrence of obesity and cardiometabolic changes in some groups requires prolonged surveillance.

The results of DAWNING and NADIA also showed relevant implications for health systems with limited access to genotyping. Dolutegravir demonstrated high efficacy after failure of regimens based on non-nucleoside reverse transcriptase inhibitors, and NADIA indicated that maintaining tenofovir could produce high suppression even in the face of expected resistance, when combined with a high genetic barrier drug (31,32). These data may simplify second-line protocols, but they do not eliminate the importance of monitoring viral load, adherence, and investigating persistent failure.

In people with advanced immunosuppression, the REALITY study's expanded prophylaxis package reduced mortality, tuberculosis, cryptococcosis and hospitalizations (33). The benefit showed that starting antiretroviral therapy, although essential, may not be sufficient in the first weeks of treatment for people with very low CD4 counts. The temporary combination of prophylaxis against opportunistic infections can reduce early mortality. Because the intervention included several medications, it was not possible to identify which component provided the greatest benefit, and the added pill burden should be considered.

Community-based interventions showed more variable results. HPTN 071 PopART and the Botswana Combination Prevention Project identified a reduction in incidence in certain arms, while SEARCH and ANRS 12249 TasP did not demonstrate a significant difference between the intervention and standard care (34-37). This inconsistency does not invalidate the effectiveness of diagnosis and treatment. It highlights the gap between individual efficacy and population impact. For therapy to reduce community incidence, it is necessary to achieve successively people not diagnosed, confirm the diagnosis, link them to the service, start treatment, maintain adherence, and achieve viral suppression. Losses at any stage reduce the final effect.

The limited contrast between groups also influenced community trials. During the conduct of multiple studies, national guidelines came to recommend universal treatment, increasing the availability of therapy in control communities. Population mobility, cross-area contamination, low engagement, and the small number of clusters also limited the ability to detect differences. Thus, the absence of significant reductions in some trials should be interpreted as implementation and programmatic differentiation challenges, and not as an absence of treatment effect on transmission.

Rapid start or same-day strategies improved therapy initiation, retention, and viral suppression in RapIT and in the trial conducted in Haiti (38,39). These findings indicated that multiple preparatory visits may create avoidable barriers, especially in populations with transportation difficulties, work and income constraints, or stigma. However, immediate initiation should be accompanied by suf-

ficient clinical assessment to identify opportunistic infections that require prior management or modification of the timing of therapy introduction. Simplifying care should not mean reducing clinical safety.

The association observed by Tanser et al. between greater community coverage of antiretroviral therapy and lower individual risk of acquisition provided complementary population-level evidence to randomized trials (40). Although the observational design is subject to residual confounding, the relationship between coverage and risk reduction was biologically plausible and consistent with treatment as prevention. The result reinforced that expanding therapy produces collective benefit in addition to individual benefit.

From a global perspective, the findings showed that available technologies are capable of substantially reducing incidence, vertical transmission, mortality, and clinical progression. The main contemporary limitation seems to lie less in the absence of effective interventions and more in the unequal distribution of these interventions. Populations with greater vulnerability often face barriers of cost, criminalization, stigma, discrimination, distance from services, food insecurity, gender inequality, and treatment discontinuity. Biomedical strategies do not reach their potential when implemented without attention to social determinants and human rights.

The review identified as strengths the inclusion of studies conducted in different regions, populations, and levels of attention, as well as the integration of prevention, treatment, and public health from a global perspective. Separating the meta-analyses by strategy also prevented the inappropriate combination of clinically distinct interventions. Prioritizing measures adjusted in clustered and observational studies further reduced the risk of artificially precise estimates.

Among the limitations, the high heterogeneity of interventions, comparators, follow-up periods, and outcomes stood out. Some syntheses included only a few studies, preventing a reliable assessment of publication bias. PrEP trials showed important differences in adherence, while community studies were influenced by changes in guidelines and contamination between groups.

Part of the evidence of intransmissibility was derived from observational cohorts, although the consistent absence of transmissions linked to it and the broad duration of exposure strengthened the inference. Historical studies were also included with regimens currently replaced, necessary to understand the evolution of strategies, but with limited contemporary clinical applicability.

Another limitation was the inability to produce a single global measure for all interventions. This absence, however, reflected a necessary methodological decision. Combining into a single estimate PrEP, circumcision, early treatment, vertical prevention, and community interventions would yield a result without clinical or epidemiological significance. Interpretation should be conducted by intervention domain and should consider not only the magnitude of efficacy, but also adherence, safety, feasibility, equity, and implementation capacity.

In summary, the results indicated that controlling HIV requires a combined, needs-centered approach for populations. Long-acting PrEP, early initiation of therapy, sustained viral suppression, vertical prevention, and expanded testing are complementary components. No single strategy is sufficient to respond to global epidemiological diversity. The greatest impact will be achieved when highly effective interventions are offered in an accessible, continuous, culturally appropriate, and integrated manner within health systems capable of reducing losses throughout the entire prevention and care cascade.

CONCLUSION

This systematic review showed that the global response to HIV depends on the coordination of preventive, therapeutic, and public health strategies, with outcomes determined not only by the biological effectiveness of the interventions, but also by adherence, access, continuity of care, and the capacity of health systems to implement them. The evidence analyzed confirmed consistent benefits from pre-exposure prophylaxis, voluntary medical male circumcision, early initiation of antiretroviral therapy, treatment as prevention, prevention of mother-to-child transmission, and expanded diagnosis and linkage to care.

A PrEP oral reduced significantly reduced HIV acquisition, although its effectiveness varied according to adherence. The injectable, twice-yearly regimens showed higher magnitudes of protection than the oral modalities in the trials assessed, indicating potential to overcome barriers related to daily use. However, incorporating these technologies requires infrastructure, regular follow-up, resistance monitoring, and policies that ensure equitable access.

Male circumcision showed a consistent reduction in heterosexual acquisition of HIV by men and should be understood as a complementary component of combination prevention. Early antiretroviral treatment reduced serious events, tuberculosis, mortality, and sexual transmission, while cohorts of serodiscordant couples reported no transmissions genetically linked during periods of sustained viral suppression. These findings reinforced the principle that maintaining an undetectable viral load prevents sexual transmission of HIV under the conditions studied.

Combined antiretroviral therapy has also transformed prevention of mother-to-child transmission, enabling rates below 2% in settings of timely diagnosis, adherence, and adequate follow-up. However, the elimination of vertical transmission remains dependent on integration between antenatal care, early initiation of treatment, viral load monitoring, neonatal prophylaxis, and keeping the mother and child engaged in care.

Regimens containing dolutegravir showed high virological efficacy in both initial treatment and after therapeutic failure, although weight gain and possible cardiometabolic effects indicated the need for prolonged monitoring. Among people with advanced disease, the combination of antiretroviral therapy and expanded prophylaxis against opportunistic infections reduced early mortality, highlighting the importance of additional interventions for individuals with severe immunosuppression.

Community-based strategies produced heterogeneous epidemiological results. The greatest benefits were observed when expanded testing was accompanied by effective linkage, timely initiation of therapy, retention in care, and viral suppression. The lack of incidence reduction in certain trials primarily reflected imp-

lementation limitations, contamination between communities, low differentiation between groups, and losses along the care cascade.

It was concluded that the tools currently available have the capacity to substantially reduce the incidence, transmission, morbidity, and mortality related to HIV.

However, the full potential of these interventions will only be achieved through health policies that address inequalities in access, stigma, discrimination, socioeconomic vulnerability, criminalization of key populations, and discontinuity in medication supply.

Sustainable control of the epidemic requires combination prevention, universal treatment, virological monitoring, expansion of long-lasting technologies, and strengthening of health systems. The strategies must be adapted to the epidemiological, cultural, and structural characteristics of each population, while preserving autonomy, equity, and human rights. In this way, the integration of biomedical innovation, continuous clinical care, and inclusive public policies is the most consistent path to reduce the global burden of HIV and move toward the interruption of its transmission.

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