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The Art of HIV Elimination: Past and Present Science

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Abstract

Introduction: Remarkable strides have been made in controlling the HIV epidemic, although not enough to achieve epidemic control. More recently, interest in biomedical HIV control approaches has increased, but substantial challenges with the HIV cascade of care hinder successful implementation. We summarise all available HIV prevention methods and make recommendations on how to address current challenges.

Discussion: In the early days of the epidemic, behavioural approaches to control the HIV dominated, and the few available evidence-based interventions demonstrated to reduce HIV transmission were applied independently from one another. More recently, it has become clear that combination prevention strategies targeted to high transmission geographies and people at most risk of infections are required to achieve epidemic control. Biomedical strategies such as male medical circumcision and antiretroviral therapy for treatment in HIV-positive individuals and as pre-exposure prophylaxis in HIV-negative individuals provide immense promise for the future of HIV control. In resource-rich settings, the threat of HIV treatment optimism resulting in increased sexual risk taking has been observed and there are concerns that as ART roll-out matures in resource-poor settings and the benefits of ART become clearly visible, behavioural disinhibition may also become a challenge in those settings. Unfortunately, an efficacious vaccine, a strategy which could potentially halt the HIV epidemic, remains elusive.

Conclusion: Combination HIV prevention offers a logical approach to HIV control, although what and how the available options should be combined is contextual. Therefore, knowledge of the local or national drivers of HIV infection is paramount. Problems with the HIV care continuum remain of concern, hindering progress towards the UNAIDS target of 90-90-90 by 2020. Research is needed on combination interventions that address all the steps of the cascade as the steps are not independent of each other. Until these issues are addressed, HIV elimination may remain an unattainable goal.

Introduction

As the HIV epidemic approaches its fourth decade, effective prevention remains elusive in the communities most affected by the virus. An estimated 36.9 million people were living with HIV globally by end 2014 [1] of whom 70% in sub-Saharan Africa. In 2014, an estimated 1.4 million people acquired HIV infection; 66% of these new infections and 66% of all HIV-related deaths occurred in sub-Saharan Africa, a region disproportionately affected by the epidemic. Remarkable strides have been made recently towards combating the epidemic and increasing antiretroviral therapy (ART) coverage with considerable reduction in mortality and morbidity [2], such that in 2014, 40% of all people living with HIV were receiving ART. Following the results of the START [3] and TEMPRANO [4] trials, the World Health Organisation (WHO) now recommends ART regardless of CD4 count [5], a policy that would maximise both the individual and population health benefit of ART. This aligns with the recent UNAIDS target of 90:90:90 (90% of people living with HIV aware of their HIV status, 90% of people diagnosed HIV-positive on ART, 90% of people on ART virologically suppressed) in 2020 [6], but will require huge financial investments and commitments from governments to bear fruit.

It is now well-recognised that prevention approaches need to be combined to accelerate the effective prevention of HIV acquisition and transmissions [7]; HIV programme planning have now moved from the implementation of single preventive methods to combination context-specific prevention approaches, for which evidence of effectiveness exists.

This paper reviews currently available HIV prevention methods, highlighting the strengths and weaknesses of past prevention approaches, draws attention to the present array of prevention armamentarium available and conceptualises how these could be combined towards the goal of HIV elimination.

HIV Prevention

Behavioural prevention

Behavioural prevention approaches include: delaying onset of first intercourse, decreasing the number of sexual partners, increasing the number of sexual acts protected, counselling and testing for HIV including repeat HIV testing, encouraging adherence to biomedical HIV prevention strategies, decreasing sharing of needles and syringes and reducing substance use [8].

A 2010 review of behavioural intervention trials, with HIV incidence as main outcome, showed no significant reduction in HIV incidence in any of the nine randomised-controlled trials studied [9]. Project Accept (HPTN 043), is a cluster-randomised trial evaluating whether a multicomponent social and behavioural prevention approach could reduce HIV incidence. In this trial community-based versus facility-based HIV counselling and testing showed no significant reduction in HIV incidence overall (relative risk [RR] 0·86, 95% CI 0·73–1·02) although there was a significant reduction in HIV incidence in he sub-group of women > 24 years of age (RR=0·70, 0·54–0·90) [10].

Structural interventions

HIV-associated structural factors are defined as the physical, social, cultural, organizational, community, economic, legal or policy aspects of the environment that impede or facilitate persons' efforts to avoid HIV infection [11] For example, laws that discriminate against certain HIV risk groups such as men who have sex with men (MSM) or injecting drug users may stigmatise and hinder access to HIV prevention services. Similarly, cultural norms which perpetuate gender inequity may leave women economically dependent on men and unable to negotiate condom use for fear of abandonment [12]. Interventions addressing these factors tend to be complex and context-specific; they do not seek to address risky behaviours directly, but address the prevailing circumstances which give rise to risky behaviours, acting on factors distal to the HIV outcome of interest. Distal factors may impact the outcome through multiple causal pathways making them difficult to evaluate; replication in other environments is challenging. One of the structural interventions receiving attention recently is the use of social cash transfers to encourage safer sex and a reduction in HIV acquisition. A randomised control trial in Lesotho using a lottery scheme as an incentive to reduce risky sexual behaviour showed a 25% (OR 0.75, 95% CI 0.58 – 0.97) reduction in HIV incidence over 2 years [13]. A cluster randomised trial (CRT) in Malawi showed that cash incentives to young women and their households reduced HIV prevalence by 64% at 18 months; but making the payments conditional on school attendance made no difference to the reduction in HIV infection observed [14]. However a recently concluded CRT in South Africa showed that a conditional cash transfer to young women and men tied to HIV testing, participation in life skills training and academic attainment reduced the incidence of HSV-2 by 30% but did not have an impact on HIV incidence after 24 months [15]. Similarly, another recently concluded randomised trial in South Africa found that cash transfer which is conditional on 80% school attendance by young women showed no reduction in HIV incidence after 3 years [16]. These results suggest that the effectiveness of social cash transfer could be context specific.

Treatment of sexually transmitted infections (STIs)

Substantial evidence exists from observational studies suggesting an increased risk of HIV acquisition with both curable STIs and genital herpes [17,18]. STIs have also been associated with increased HIV infectiousness, although this has not been quantified directly in observational studies [19]. HIV-STI co-infection appears more likely to result in HIV transmission than infection with HIV alone [20,21]

However, nine randomised trials to date (four cluster randomised trials, two individual randomised trials on treating curable STIs and three individual randomised trials on Herpes suppressive therapy) have together failed to confirm the hypothesis that STI treatment would reduce HIV transmission and acquisition [19]. Of the four cluster-randomised trials examining the impact of STI treatment on HIV incidence, only the Mwanza trial in Tanzania showed syndromic treatment of STIs to be associated with a 40% significant reduction in HIV incidence [22]. Various factors may explain the differences in effect between trials, including differences in the HIV epidemic phase, enhanced interventions in the control group, and higher prevalence of STIs in the Mwanza trial compared to the other sites [19].

Syndromic treatment of STIs focusses on patients presenting with symptoms, but provision of inadequate treatment and poor adherence could result in low effectiveness of syndromic treatment, which was estimated to be only 13% for curable STIs in rural KwaZulu-Natal [23]. Further, a significant proportion of STIs are asymptomatic [24] and the large pool of untreated individuals with asymptomatic STIs will continue to transmit HIV. This situation coupled with poor uptake of partner notification could result in significant rates of STI reinfections and will likely impact HIV transmission and acquisition.

The effect of herpes simplex virus (HSV) suppressive therapy on HIV incidence has been evaluated in two randomised trials; the first one in high-risk HSV-2 positive, HIV negative women in Tanzania [25] and the second involving women from three sites in Africa (Harare, Lusaka, Johannesburg) and MSM from Peru and the USA [26]. In these trials, treating HIV negative, HSV-2 positive individuals with aciclovir did not result in decreased HIV acquisition. A third randomised trial investigated the impact of HSV-2 suppressive therapy in HIV positive individuals on the risk of HIV transmission. Although suppressive therapy with acyclovir reduced HIV plasma viral load by about 0.25 $\log^{10}$ and genital ulcers due to HSV-2 by 73%, there was no significant effect on HIV transmission (RR 0.92, 95% CI 0.60-1.41).

Although, these results are disappointing there remains compelling biological and epidemiological evidence that STIs are co-factors for HIV acquisition and transmission [27] and treatment of STIs should be part of the HIV care and prevention programme.

Male circumcision

A meta-analysis of 27 published observational studies on male circumcision in sub-Saharan Africa [28] provided evidence that male circumcision protects against HIV acquisition.

Male circumcision was shown to be protective against HIV acquisition in three randomised controlled trials in South Africa, Uganda and Kenya [29-31]; in pooled analysis the combined incidence risk ratio (IRR) at 12 months was 0.50 (95% CI 0.34-0.72) and 0.46 (95% CI 0.34-0.62) at 21 or 24 months [32].

These observations in heterosexual HIV acquisition raised the question of whether this protection would also be observed in MSM. However, an observational analysis of data from a randomised controlled trial of HSV-2 suppressive therapy to prevent HIV acquisition found no evidence that circumcision was associated with reduced HIV incidence in MSM who practised predominantly insertive sex (RR 0.31, 95% CI: 0.06-1.51) [33]

Non-ART vaginal microbicides

Initial research involving microbicides focused on non-ART related compounds, with a recent shift to ART-related compounds following multiple failures of the former to demonstrate effectiveness in the prevention of HIV acquisition in women.

These earlier compounds were surfactants (nonoxynol-9) which disrupt the cell membranes of bacteria and viruses, polyanions (Carraguard, cellulose sulphate and PRO 2000) which interfere with the attachment of the virus to target cells in the mucosa and vaginal milieu, and protectors (BufferGel) which render the vagina acidic. In an acidic environment, sperms and viruses are inactivated or killed [34]. A recent meta-analysis of 13 randomised controlled trials involving 35,905 HIV negative women from Africa, India, Thailand and the United States of America between 1996 -2011 showed no protective effects on HIV acquisition (RR 0.97, 95% CI: 0.87-1.08) [35]. This meta-analysis included mostly non-ART related microbicides; five trials of nonoxynol-9, two trials of SAVVY, two of cellulose sulphate, one of Carraguard, one of PRO 2000 and one of BufferGel and one ART-related microbicide (CAPRISA 004 with 1% vaginal tenofovir gel). More adverse events due to genital lesions were reported in the nonoxynol-9 trials while these events were similar in both the microbicide and placebo arms of the other trials.

Antiretroviral treatment

The efficacy of antiretroviral therapy at preventing HIV transmission has been demonstrated in a variety of clinical scenarios such as in the prevention of mother-to-child [36,37], and heterosexual transmission [38], which led to the declaration that an HIV infected individual who is on ART and has undetectable viral loads for at least 6 months with no STIs is sexually non-infectious [39]. Other uses include post-exposure prophylaxis in HIV-negative individuals after occupational or sexual exposure to body fluids from known or suspected HIV-positive individuals [40-43].

Oral and topical ART-based pre-exposure prophylaxis: More recently, studies have shown that ART could also be used by HIV-negative individuals prior to exposure to HIV to prevent HIV acquisition, known as pre-exposure prophylaxis (PrEP).

Table 1 summarises the 11 trials on pre-exposure prophylaxis using

Author	Study setting	Sample size contributing data	Study Population	Intervention/Control	Follow-up time/Person years	HIV seroconversions	Impact on HIV incidence (95% CI)
Peterson, L 2007[44]	Ghana, Cameroun, Nigeria	936	18-35 year old high risk HIV negative women	Intervention: Oral daily tenofovir (TDF) Control: Placebo	476	Intervention: 2 Control: 6	Rate ratio (RR) 0.35 (0.03-1.93)
Abdool Karim, Q 2010[45] (CAPRISA 004)	South Africa	889	18-40 year old HIV-negative women	Intervention: coitally administered 1% vaginal gel formulation of TDF Control: Placebo	1341	Intervention:38 Control:60	RR 0.61(0.40-0.94)
Grant RM, 2010[51] (iPrEX study)	Peru, Ecuador, South Africa, Brazil, Thailand, USA	2499	>18 years, HIV negative MSM or transgender	Intervention: Oral daily tenofovir/emtricitabine (TDF-FTC) Control: Placebo	3324	Intervention: 36 Control: 64	44% reduction (15-63)
Thigpen MC, 2012[52] (TDF2 Study)	Botswana	1219	18-39 years, HIV negative men and women	Intervention: Oral daily TDF-FTC Control: Placebo	1563	Intervention:9 Control:24	62.2% reduction (21.5-83.4)
Baeten J.M, 2012[53] Partners PrEP Study	Kenya, Uganda	4747	Heterosexual HIV serodiscordant couples	Interventions: i) Once daily oral TDF ii) Once daily TDF-FTC Control: Placebo	7830	Interventions: TDF 17 TDF/FTC: 13 Control: 52	67% reduction due to TDF (44-81) 75% reduction due to TDF/FTC (55-87)
Van Damme L, 2012[46] FEM-PrEP Study	Kenya, South Africa, Tanzania	2056	18-35 years, HIV negative women	Intervention: Oral daily TDF-FTC Control: Placebo	1407	Interventions: 33 Control: 35	Hazard ratio (HR) 0.94 (0.59-1.52)
Marrazzo J, 2013[54] VOICE Study	South Africa, Zimbabwe, Uganda	5029	Mean age 25.3 years, HIV negative women	Intervention: i) Oral daily TDF ii)Oral daily TDF/FTC iii) 1% TDF vaginal gel Control: i) Oral placebo ii) Placebo vaginal gel	5509	Interventions: i) oral TDF 52 ii) oral TDF-FTC 61 iii) Vaginal TDF gel: 61 Control i) Placebo for oral TDF: 35 ii) Placebo for oral TDF/FTC: 60 iii) Placebo for vaginal gel: 70	HR for Oral TDF 1.49 (0.97-2.3) HR for oral TDF/FTC 1.04 (0.7-1.5) HR for vaginal TDF gel 0.85 (0.6-1.2)
Choopanya K, 2013 [55] Bangkok Tenofovir study	Bangkok, Thailand	2413	20-60 years, HIV negative and reported injecting drug use within the past year	Intervention: Oral tenofovir Control: Placebo	9665	Intervention: 17 Placebo: 33	Efficacy of tenofovir 48.9% (9.6-72.2)
Rees H, 2015 FACTS 001	South Africa	2029	HIV negative women, 18-30 years	Intervention: Pericoital 1% vaginal gel formulation of Tenofovir Control: Placebo	3036	Intervention: 61 Control: 62	IRR 1.0 (0.7-1.4)
McCormack S, 2015 PROUD	England	544	HIV negative MSM, ≥18 years	Immediate: oral daily TDF/FTC Deferred: Oral daily TDF/FTC after 12 months	465	Immediate: 3 Deferred: 20	86% reduction (64-96)
Molina J-M, 2015 IPERGAY	France, Canada	400	HIV negative adult MSM	Intervention: On demand TDF/FTC Control: Placebo		Intervention: 2 Control: 14	86% reduction (39.4-98.5)

Table 1: Oral and ART-based topical pre-exposure prophylaxis.

ART completed to date. The first trial evaluating the effectiveness of once daily oral tenofovir for pre-exposure prophylaxis was conducted in three sites in Ghana, Cameroun and Nigeria among high risk HIV-negative women aged 18-35 years [44]. The Nigeria and Cameroun sites were closed prematurely for unspecified reasons and as a result this trial lacked statistical power because of the small number of HIV seroconversions observed. In the CAPRISA 004, a proof-of-concept phase II trial including 889 HIV negative women, 1% tenofovir gel compared to placebo was shown to significantly decrease HIV acquisition, (RR 0.63, 95% CI 0.43-0.93) [45]. However, the results of three other PrEP trials, FEM-PrEP [46] , VOICE [47] and FACTS 001 [48] conducted in women have been very disappointing with none of them demonstrating any efficacy. Substudies of adherence within these large trials showed that there was poor adherence to the study drug which could explain the lack of efficacy observed.

The placebo arm of two other PreP trials – IPERGAY [49] and PROUD [50] - were terminated early because of marked reduction in HIV acquisition in the intervention arm compared to the placebo arm

ART in HIV-discordant partnerships: Table 2 summarises the nine observational studies and one randomised-controlled trial evaluating the effectiveness of ART in preventing HIV transmission from the index to the HIV-uninfected partner. A Cochrane review and meta-analysis [56] of these observational studies identified 2112 HIV transmissions: 1,016 among ART-treated couple and 1096 in those not taking ART. The combined rate ratio for the nine observational studies was 0.58 (95% CI: 0.17-0.75).

The one trial was a multicentre randomised-controlled trial (HPTN 052) [38] involving 1763 stable serodiscordant couples from 9 countries (Table 2) which reported findings in 2011. HIV infected individuals with CD4 counts between 350-550 cells/µL and in a stable relationship with an uninfected partner were randomly allocated to receive ART immediately (early therapy) or delayed until CD4 count decreased below 250 cells/mm³ or development of clinical symptoms (deferred therapy). This study was stopped early because of clear efficacy of ART in preventing transmission in the early therapy arm. There were 39 HIV transmissions in total of which 28 were virologically linked to the infected partner; of the linked transmissions, 27 occurred in the deferred and one in the early therapy group (HR 0.04, 95% CI: 0.01-0.27). Besides the clear public health significance of this finding, there was also a clinical benefit to the individual if randomised to the early therapy arm.

An earlier meta-analysis [57] reviewed observational studies of HIV transmission involving individuals on and not on ART from 11 cohorts comprising 5021 heterosexual couples and 461 HIV

Author	Study setting	No of couples	Study population	Study design/ intervention	Follow-up duration in person years	ART status of index case &sero-conversions (n)	Effect estimate (95% CI)
Musicco, M 1994[62]	Italy	436	Female sexual partners of HIV-infected males majority of whom were injecting drug users	Observational/ Zidovudine (ZDV) monotherapy	740	Partners of men not on ZDV:21 Partners of men on ZDV: 6	Risk lower in partners of treated Men RR 0.50 (0.1-0.9)
Melo MG, 2008[63]	Brazil	93	Female index case: 67 Male index case: 26	Observational/ 41 on triple ART 52 not on ART	Not stated	Partner on ART: 0 Partner not on ART : 6	Risk lower if partner on ART RR 0.10 (0.01-1.67)
Sullivan P, 2009[64]	Rwanda, Zambia	2993	HIV discordant couples	Observational	5609	Partner on ART: 4 Partner not on ART: 171	Risk lower if partner on ART RR 0.21 (0.08-0.59)
Del Romero, J 2010[65]	Spain	424	Stable sexual couples	Observational *144 couples with index partner on triple ART *47 couples on mono/dual ART *341 couples with index partner not on ART	1355	Partner on ART: 0 Partner not on ART: 5	Risk lower if partner on ART RR 0.21 (0.01-3.75)
Donnell D, 2010[66]	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	3381	HIV serodiscordant partners	Prospective cohort 349 initiated ART 3082 did not initiate ART	4831	Partner on ART: 1 Partner not on ART: 102	Risk lower if partner on ART 0.08 (0.00-0.57
Lu W, 2010[67]	China	1927	HIV serodiscordant couples Male index 1092 Female index 835	Prospective cohort 1369 on ART 558 not on ART	4918	Partner on ART: 66 Partner not on ART: 18	RR 1.44 (0.85-2.44)
Reynolds SJ, 2011[68]	Uganda	250	HIV discordant couples Male index: 145 Female index: 155	Prospective cohort 32 initiated ART 218 not on ART	513	Partner on ART: 0 Partner not on ART: 42	RR 0.10 (0.01-1.64)
Cohen MS, 2011[38]	Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand, USA	1763	Stable HIV-discordant 97% heterosexual	Randomised controlled Immediate versus deferred ART	3152	Early therapy: 1 Deferred therapy: 27	RR 0.04 (0.01-0.27)
Birungi J, 2012 [69]	Uganda	586	Serodiscordant couples	348 ART-eligible couples initiated 238 not eligible for ART	Median follow up of 1.3 years	ART group : 9 Non-ART group: 8	RR 0.91 (0.38-2.20)
Jia Z, 2012 [70]	China	38, 862	Serodiscordant couples	24057 ART-treated 14,805 non-ART group	101,295	ART-group: 935 ART-naïve: 696	RR 0.74 (0.65-0.84)

Table 2: ART for preventing HIV transmission in HIV discordant partnerships.

transmission events. The HIV transmission risk in the five studies of individuals on ART, irrespective of viral load, was 0.46 (95% CI: 0.19-1.09) based on five transmissions and 1098 person years of follow up. When this meta-analysis was restricted to the two studies in which individuals had undetectable viral load, no transmission was recorded in 291 person years of follow up with an upper confidence limit of 1.27 per 100 person years.It is now established that ART is effective at preventing transmission in stable heterosexual couples, it remains unknown whether ART will be similarly effective at preventing HIV transmission at the population level. An observational study from rural KwaZulu-Natal suggests this to be the case [58]; and this question is currently being addressed by four randomised trials [59-61].

HIV vaccines

Recent HIV vaccine research has focused on antibody-based strategies following isolation of potent highly broadly neutralising monoclonal antibodies from infected individuals [71]. However, both arms of the adaptive immune system have important roles to play against HIV infection and or disease [71,72]. Neutralising antibody response aim to prevent acquisition of HIV infection, while cytotoxic T lymphocytes (CTL) response, which only recognises infected host cells, could play a role in controlling viral replication and disease progression. It is unclear if robust CTL response can eradicate HIV infection in humans [71].

Only one of the six HIV vaccine trials completed to date showed a protective efficacy (Table 3).

The VAX004 (North America and the Netherlands) and VAX003 (Thailand) were protein subunit trials using rgp120 monomers as immunogens aiming to elicit neutralising antibodies. Both failed to show significant protection against HIV acquisition [73,74].

Another vaccine approach is based on recombinant viral vectors engineered to express the gene of interest. The recombinant adenovirus serotype 5 was used as the vector for the Step (North and South America, the Caribbean and Australia) and Phambili (South Africa) trials [75,76]. These trials assessed the ability of these vaccines to stimulate the cellular immune responses. The Step trial was terminated early on the grounds of futility and lack of control of early viraemia in those who became infected. Enrolment in the Phambili trial was stopped because of the results observed in the Step trial.

The HVTN 505 (USA), was a phase 11b DNA vaccine trial that evaluated a DNA prime expressing Gag, Pol, Nef and Env with a recombinant adenovirus serotype 5 boost expressing Gag, Pol and Env. This trial was also halted prematurely for futility [77].

The RV144 vaccine trial in Thailand employed a combination of vaccine approaches [78], comprising a canary pox viral vector prime expressing Env, Gag and Pol followed by a protein subunit vaccine boost (AIDSVAX B/E). The vaccine efficacy was 31% (95% CI, 1.1 to 52.1) after 3.5 years. To date, this remains the only vaccine trial to demonstrate some protection against HIV acquisition.

Mathematical modelling

Mathematical modelling has played a pivotal role in the understanding of HIV pathogenesis by elucidating virus kinetics in terms of virus production and clearance from blood and CD4 T-lymphocytes depletion [80,81]. This showed that HIV replicated at a very rapid rate and demonstrated the superiority of combination therapy over single drug therapy on virus kinetics. This early models also examined the role of long-lived and latently infected cell populations in the blood and the question as to whether combination therapy would be adequate to eradicate or cure HIV in an individual arose as a hypothesis. Later models have identified third and fourth phase decays in HIV kinetics through the use of single copy assays [82]. This discovery as opposed to the initial two-phase decay proposed in earlier models implies that combination therapy may not be sufficient to eliminate HIV within an individual.

Models have also played significant roles in generating important hypothesis about the impact of immediate ART on HIV elimination from the general population. The model by Granich et al. [83] generated a lot of interest in this regard. This model predicted that yearly HIV testing followed by immediate ART coupled with male circumcision, behaviour change programmes, condoms and treatment of STIs could reduce HIV incidence to less than one case per 1000 per year within 10 years and reduce the prevalence of HIV to less than 1% within 50 years. However the assumptions used to parameterise the model may be overly optimistic as the impact of such approaches have been shown by more recent models to be sensitive to factors such as uptake of HIV testing, linkage to care and ART coverage and the nature of the sexual networks [84-86]. There are challenges in achieving the sort of coverage required as illustrated by the leaks in the HIV care cascade described below.

Mathematical models, in combination with empirical research would play pivotal role in understanding interventions and their expected impact on HIV prevention and elimination.

Barriers to HIV Elimination

HIV care cascade

For ART to succeed as an effective HIV prevention method, there

Author	Vaccine trial (randomised-placebo controlled	Vaccine type	Sample size	Population	Phase	Intended immune response	Results
Flynn et al; 2005 [73]	VAX004	Protein: rgp120	5400	Mostly high-risk MSM	III	Antibodies, CD4+ T cells	6% (-17 to 24)
Pitisuttithum et al; 2006 [74]	VAX003	Protein: rgp120	2500	Injection drug users	III	Antibodies, CD4+ T cells	0.1% (-30.8 to 23.8)
Rerks-Ngarm et al; 2009 [78]	RV144	Pox/protein: ALVAC/grp120	16,403	Low risk heterosexuals	III	Antibodies, CD4+ & CD8 T cells	31% (1.1-52.1)
Buchbinder, SP et al; 2008 [75]	HVTN 502/Merck 023 (STEP)	Adenovirus type 5 (Ad5) gag/pol/nef	3000	High risk MSM, heterosexual men and women	IIb	CD8+ & CD4+ T cells	HR 1.2 (0.6-2.2)
Gray et al; 2011b [76]	HVTN 503 (Phambili)	Ad5 gag/pol/nef	801; original target of 3000	Heterosexual men and women	IIb	CD8+ & CD4+ T cells	HR 1·25 (0·76-2·05)
Hammer, S 2013 [79]	HVTN 505	DNA-Ad5 gag/pol/nef/env	2504	High risk MSM	IIb	Antibodies, CD4+ & CD8+ T cells	-25% (-121.2 to 29.3)

Table 3: Summary of HIV vaccine trials and outcomes.

needs to be good coverage in all the steps of the HIV care pathway. The entry point into this pathway is HIV testing. Those testing HIV-positive need to be willing to initiate ART even when not clinically indicated for their own health, retained in care and be adherent lifelong. Equally important are those who tested negative. They should be aware of methods to protect themselves from HIV acquisition and be willing to test for HIV repeatedly for those who become HIV-positive to be linked to the care pathway.

HIV testing and linkage to care

HIV testing is necessary for linkage to HIV care and treatment. For HIV elimination, large numbers of individuals have to be willing to test for HIV regularly and those testing positive need to be linked to care and started on ART. However, despite the availability of effective treatment for HIV, 36% of individuals in SSA have never been tested for HIV [2], with low perception of risk, concerns about confidentiality and fear of disclosure, stigma and discrimination suggested as explanations. Gender inequity that leaves women economically dependent on men may undermine the ability of women to seek HIV testing [87-89].

Further, studies have shown a huge drop between the numbers of people taking an HIV test and linked to care. A systematic review and meta-analysis of eleven studies in SSA estimated that only 57% (95% CI, 48-66) of those diagnosed HIV positive are linked to care [90]. Another meta-analysis of studies in the USA estimated that 69% (95% CI, 66-71) of individuals diagnosed with HIV entered into care averaged over the time intervals from 1995 to 2009 [91]. Substantially higher numbers of individuals need to be linked to care for treatment assessment to realise the goal of HIV elimination. In a review of studies examining the barriers to linkage, the most commonly identified factors include transport costs and distance to clinics. Others include concerns about disclosure and stigma, staff shortages, long clinic waiting times, male sex and younger age [92].

Adherence/Retention in Care

The WHO defines adherence as "the extent to which a person's behaviour-taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [93]. Adherence to ART is vital for viral suppression [94], which is important for optimal treatment outcomes and for prevention of HIV transmission [95]. Studies reporting on routine treatment programmes with differing ART initiation CD4 thresholds have shown that individuals starting treatment at higher CD4 counts are less likely to adhere consistently than individuals starting at lower CD4 counts [96,97]. However in the HPTN 052 on stable sero-discordant couples, adherence measured by pill count of at least 95% was seen in 79% of participants in early therapy group (CD4 350-550 cells/mm³) compared to 74% in the delayed therapy group (CD4<250 cells/mm³) [38]. This may not be reflective of real life situations. It remains to be seen how evidence from the START [3] and TEMPRANO [4] trials which suggest individual benefit to early ART would influence adherence.

In the pre-exposure prophylaxis studies in which participants were aware that they were using the prescribed medications to prevent HIV transmission, adherence measured by drug levels was poor [46,54]. A meta-analysis involving 37 qualitative and 47 quantitative studies on barriers and facilitators to adherence identified fear of disclosure, concomitant substance abuse, forgetfulness, suspicions of treatment, complex regimens, high pill burden, decreased quality of life, work and family responsibilities, falling asleep and access to medications as the main adherence barriers [98]. Retention in HIV

care takes two forms: pre-ART retention refers to retention in care of individuals not yet eligible for ART while retention on ART refers to individuals who remain in care after initiating ART. A review of four studies in South Africa and one in Malawi estimated that the median proportion of patients retained in pre-ART care was 45% when CD4 eligibility threshold was 200 cells/mm³ [90]. A review of 14 studies reporting proportions of patients retained in care from ART eligibility to ART initiation estimates a median of 68% (range 14-84%) [99]. For retention in care after initiating ART, a systematic review of 33 studies reporting on 39 patient cohorts estimated that 65% of patients are retained in ART care (range 58%-72%) after 36 months [100]. Factors that impact retention in care include challenges that relate to housing, transportation to clinics, mental health and drug abuse which would need to be addressed in affected individuals. Provider-patient relationship and clinic opening hours are other issues that need to be addressed to improve retention in care [91].

Virological failure and drug resistance

Initiation of treatment early in the course of infection before symptoms develop results in large proportions of HIV-infected individuals on ART; if adherence is indeed sub-optimal, this could lead to significant rates of virological failure and the likely development of drug resistance. Studies in sub-Saharan Africa of people who started treatment on the basis of conservative guidelines showed that 15-25% of patients had HIV-RNA >400 copies/mL 6-36 months after starting ART [101], consistent with findings from the Hlabisa HIV Treatment and Care programme with an estimated 15% of patients having HIV RNA >400 copies/mL 12 months after starting ART [102]. A further study from this latter cohort showed that 86% of individuals failing first-line ART with detectable VL had at least one drug-resistant mutation [103] with high levels of NNRTI- (83%) and NRTI-(81%) associated mutations; the median time spent on a failing regimen was 27 months (IQR 17-41). The long duration spent on failing ART with accumulation of resistant mutations could be a possible explanation for the 15% of patients with virological failurewhose second-line regimen was compromised.

With increasing exposure of larger numbers of people to longer durations of ART, those developing ART resistance could potentially transmit resistant virus to their sexual partners, which would result in increasing numbers of new infections due to resistant virus [104,105]. A recent evaluation of transmitted resistance in 11 regions in six sub-Saharan African countries including South Africa estimated prevalence of transmitted drug resistance in South Africa of 1.1%, but 12.3% in Kampala, Uganda [106]. Increasing prevalence of transmitted resistance would necessitate more complex and more expensive first-line regimen which could impact on adherence and result in lack of virological suppression and increased transmissions making HIV elimination difficult.

Risk compensation

HIV has become a chronic condition, and some individuals may be less concerned about HIV than thirty years ago [107], which, coupled with the knowledge that ART may prevent HIV transmission, could lead to increased high risk sexual behaviour, known as risk compensation. However, studies in resource-limited settings with high HIV prevalence have not shown an increase in risky sexual behaviour amongst individuals initiating ART. In a Ugandan study , an increase in sexual activity following ART was accompanied by a 70% reduction in the number of unprotected sexual acts with a partner known to be HIV negative or of unknown serostatus [108]. In a longitudinal study in

South Africa on HIV-infected individuals with pre-ART and post-ART follow-up over seven years, high risk sexual behaviour following ART initiation was reduced [109]. A recent ecological study from a rural South African surveillance site found no evidence of an increase in high risk sexual behaviour at the population level following the expansion of ART availability, instead there was an increase in reported condom use at last sex with regular partners [110].

However, many studies in MSM in the developed world have shown an increase in high risk sexual behaviour following the introduction of ART coinciding with an increase in HIV incidence [111,112]. Whilst the frequency of HIV testing increased during this period, this was not sufficient to account for the observed increase in the number of new diagnoses [112].

As ART roll-out in sub-Saharan Africa is relatively recent, it is important to maintain on-going surveillance in risk behaviour in this region as this may change as more people become aware of the benefit of ART to prevent transmission.

Conclusion

Remarkable strides have been made in the past decade in potentially curbing the HIV epidemic, although numbers of new infections remain unacceptably high. No HIV prevention approach is 100% efficacious; all require behaviour change as individuals need to have the agency to decide which of the prevention methods best meet their needs at any particular point in time. The optimal way to tackle the epidemic is likely to be through combination HIV prevention [113,114], which combines behavioural change, treatment of STIs, ART for HIV positives and for pre-exposure prophylaxis for HIV negatives, male medical circumcision and structural approaches (Figure 1). It is now recognised that even within generalised epidemics, there are many microepidemics, hence interventions need to be focussed in nature by targeting areas of high transmission geographies and people at most risk of infections including key populations [115]

Which and how these interventions are combined may vary by setting using the "know your epidemic, know your response" concept [116]. A modelling study calibrated using the Kenyan HIV epidemic showed that combination of interventions which are deployed in a focused manner as opposed to a uniform manner with a fixed budget applied to both scenarios resulted in more substantial decrease in the incidence of HIV infections [117]. This focused intervention approach requires that the HIV epidemic in a particular setting is characterised to subnational level. The partner demonstration project, which included high risk serodiscordant couples in Kenya and Uganda combined ART given to the HIV positive partner with PrEP given to the HIV negative partner resulted in a 96% reduction in HIV transmission from the HIV positive to the HIV-negative partner.

Research is needed into how the cascade of care can be strengthened from the point of HIV testing to linkage of individuals to care and virological suppression. This would be necessary steps to maximise the impact the new WHO guidelines which recommend ART regardless of CD4 count [5].

Factors which act as barriers and facilitators for each step of the cascade need to be understood both at the individual and health care system level so that appropriate interventions can be put in place.

Novel drug formulations that require infrequent administration would be a welcome addition to the HIV prevention armamentarium, as this strategy has the potential to increase adherence [118].

Although the HIV vaccine field has been disappointing with no sufficiently efficacious vaccine currently available, lessons have been learnt from the research with improved insight as to how HIV evades the immune system. This is not the time to relax, rather to intensify efforts in this area because an efficacious preventive vaccine would be required in addition to other biomedical intervention in order to make HIV elimination an attainable goal. The vaccine efficacy required to achieve this would need to be modelled in combination with other prevention approaches [119]. Substantial investments with smart health-financing, integrating of health services and political commitment would be required to achieve the goal of HIV elimination [119].

Figure 1: Combination interventions required to eliminate HIV.
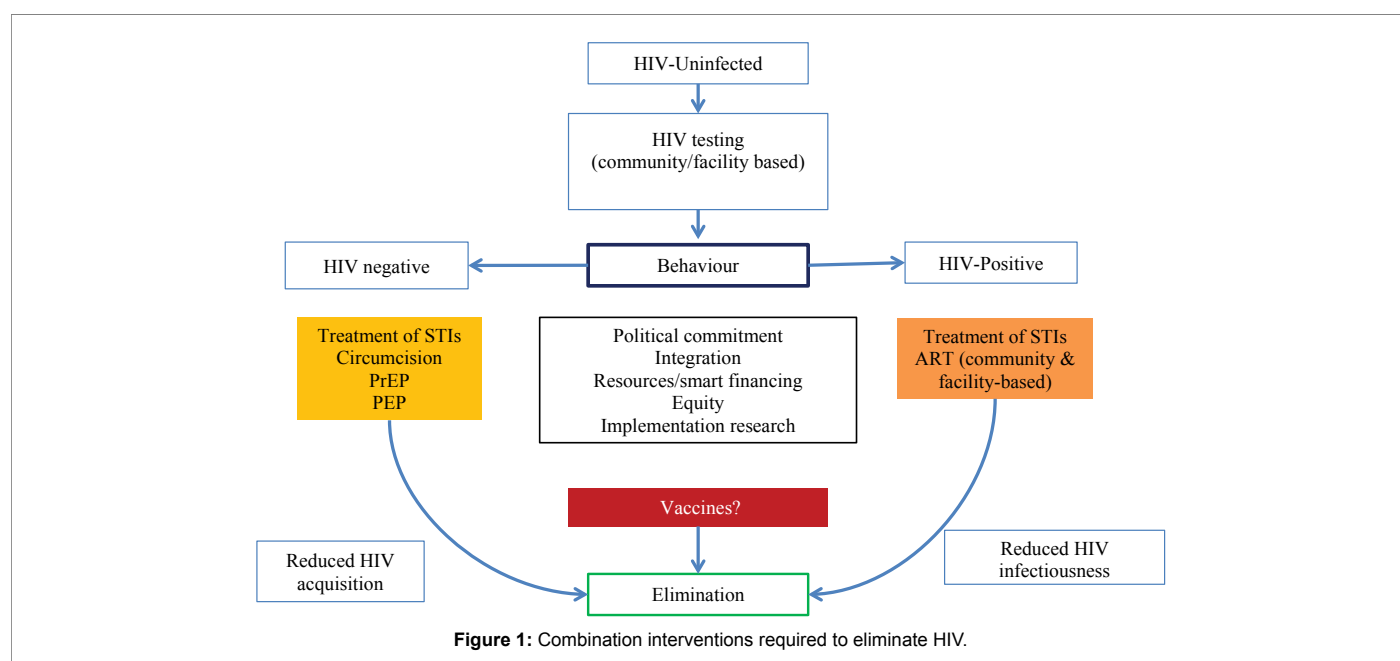
Competing interests

CI has received honoraria for services rendered to Gilead Sciences. All other authors declare no competing interest.

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Authors contributions

CI did the literature search and wrote the first draft of the review. NM, TDO, KP, DP,MF, MN and MLN extensively reviewed the article and made substantial contributions that improved the overall quality of the work. All the authors read and approved the final version of the manuscript.

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