HIV epidemiology, prevention, treatment, and implementation strategies for public health

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The global HIV response has made tremendous progress but is entering a new phase with additional challenges. Scientific innovations have led to multiple safe, effective, and durable options for treatment and prevention, and long-acting formulations for 2-monthly and 6-monthly dosing are becoming available with even longer dosing intervals possible on the horizon. The scientific agenda for HIV cure and remission strategies is moving forward but faces uncertain thresholds for success and acceptability. Nonetheless, innovations in prevention and treatment have often failed to reach large segments of the global population (eg, key and marginalised populations), and these major disparities in access and uptake at multiple levels have caused progress to fall short of their potential to affect public health. Moving forward, sharper epidemiologic tools based on longitudinal, person-centred data are needed to more accurately characterise remaining gaps and guide continued progress against the HIV epidemic. We should also increase prioritisation of strategies that address socio-behavioural challenges and can lead to effective and equitable implementation of existing interventions with high levels of quality that better match individual needs. We review HIV epidemiologic trends; advances in HIV prevention, treatment, and care delivery; and discuss emerging challenges for ending the HIV epidemic over the next decade that are relevant for general practitioners and others involved in HIV care.

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Introduction

Over the past two decades, the HIV response has made remarkable progress in understanding, preventing, and treating HIV, with incidence decreasing considerably in most areas of the world, and large improvements in life expectancy in people on antiretroviral therapy (ART). We understand more than ever before about the pathogenesis of HIV and nature of the latent reservoir, which have implications for both cure and vaccine strategies. New efficacious, robust, and more convenient biomedical technologies continue to be developed with the potential to make both HIV prevention and treatment simpler. These include long-acting oral and injectable formulations that offer alternatives to daily medications. Multisectoral investments in HIV have yielded substantial results with these tools in hand. As of 2022, 29·8 of the over 39 million people living with HIV (PLWH) were receiving treatment (up from 7·8 million in 2010), new infections have fallen by 59% since their peak, and deaths have dropped by 69%.[1]

However, the HIV epidemic remains formidable and several complex challenges are yet to be solved. Both preventive vaccines and a cure, if either prove possible, are years or perhaps decades away. In addition, the risks, tolerability, and costs of a potential cure will need to be weighed against the continually improving landscape of treatment.[2,3] It has long been clear that the HIV epidemic is inextricably tied to inequities, discrimination, and human rights, but social and economic progress has been slow and discriminatory legislation is on the rise in many places. Furthermore, attention to the inadequate implementation of existing technologies has grown into its own field of scientific inquiry and this field is rapidly evolving to develop the appropriate methods and approaches to tackle these challenges.[4] In particular, clinical providers play a key part in addressing these implementation gaps for testing, prevention, and treatment for HIV given their central role in what care ultimately gets delivered. The rapidly growing and contemporaneous epidemics of non-communicable diseases (NCDs), emerging infections like COVID-19, climate change, and other concomitant social crises have grown in the public's awareness and the HIV response should now be considered within this broader context for advancing public health. If the past two decades have shown us what is possible, the coming decades will show whether the scientific community has the will and nimbleness to successfully take on new scientific and societal challenges while balancing and integrating competing but equally important priorities, to bring the HIV epidemic under control.

In this Seminar, we discuss the current state of the HIV prevention and treatment landscape, with a specific focus on the clinical, implementation, and public health issues

Search strategy and selection criteria

We searched PubMed for studies in English for the terms "HIV" or "AIDS" in combination with one or more of the following: "epidemiology", "incidence", "prevalence", "mortality", "testing", "screening", "linkage", "art initiation", "retention", "engagement", "adherence", "viral suppression", "care cascade", "prevention", "disparities", "equity", "PrEP", "cure", "remission", "reservoir", "long-acting", "resistance", "implementation strategy", "differentiated service delivery", "community-based", "home-based", "navigator", "rapid start", "mhealth", "integration", and "incentive". We focused on studies published after 2017 and prioritised reviews and meta-analyses that provided systematic overviews of relevant topics and major clinical trials and cohort studies. We searched the reference lists of these articles to identify additional studies that were relevant for this Seminar.

most relevant to generalist and HIV providers. The tremendous advances in safe and effective biomedical prevention and treatment interventions have often failed to reach large segments of the population, and this has placed greater importance on addressing the socio-behavioural and implementation determinants of clinical outcomes. Thus, considering the implementation and client-centredness of care delivery systems to ensure client needs and preferences are met has become essential for clinical decision making at the client-provider interface. With this perspective in mind, we discuss the epidemiologic trends; advances in HIV prevention, treatment, and care delivery models; and emerging challenges for delivering high quality, effective, and equitable HIV care.

Epidemiology of the HIV epidemic

Trends in the global epidemiology of HIV

In 2023, the world faces an improving, but still challenging HIV epidemic. The total number of PLWH continues to grow from 22 million in 1997, to over 39 million in 2022 (figure 1). New infections peaked in 1997 at 3·2 million, but have fallen to 1·3 million in 2022.[1] Deaths peaked in 2004 at nearly 2 million—similar to the number of confirmed COVID-19 deaths in 2020—and fell to 630 000 by 2022.[1] Tuberculosis-related mortality among PLWH has declined by 68% since 2004 from a combination of preventive therapy and ART for HIV.[1] In some southern African countries, by the early 2000s, HIV contributed to a fall in life expectancy of up to 20 years (eg, Eswatini, Lesotho, and Zimbabwe), but even the most severely affected countries have now nearly recovered pre-HIV life-expectancy trajectories.[14] Still, HIV remains the leading cause of mortality in southern Africa ahead of cardiovascular disease, malignancies, and maternal and neonatal disorders; and goals to decrease new infections and deaths by 75% in 2020 and 90% by 2030 are further off track, particularly for incidence.[15,16]

Improvements in the HIV response have occurred largely because of a historic worldwide scale-up of HIV testing and treatment. By 2022, The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that 86% of all PLWH knew their HIV status, 76% were receiving ART (figure 1), and 68% had achieved viral suppression (up from 73%, 55%, and 46%, respectively, in 2016).[16] HIV treatment is now widely available in lower-income countries, although uptake is uneven in some settings and among marginalised populations. However, the impressive progress has not quite met UNAIDS 90-90-90 targets set in 2014 for 2020, since 90% of PLWH who have been diagnosed, 81% on ART, and 73% with viral suppressed. In response, UNAIDS revamped its targets for 2025—including updating 90-90-90 targets to more ambitious 95-95-95 targets in 2020—to re-energise the global HIV response and keep it

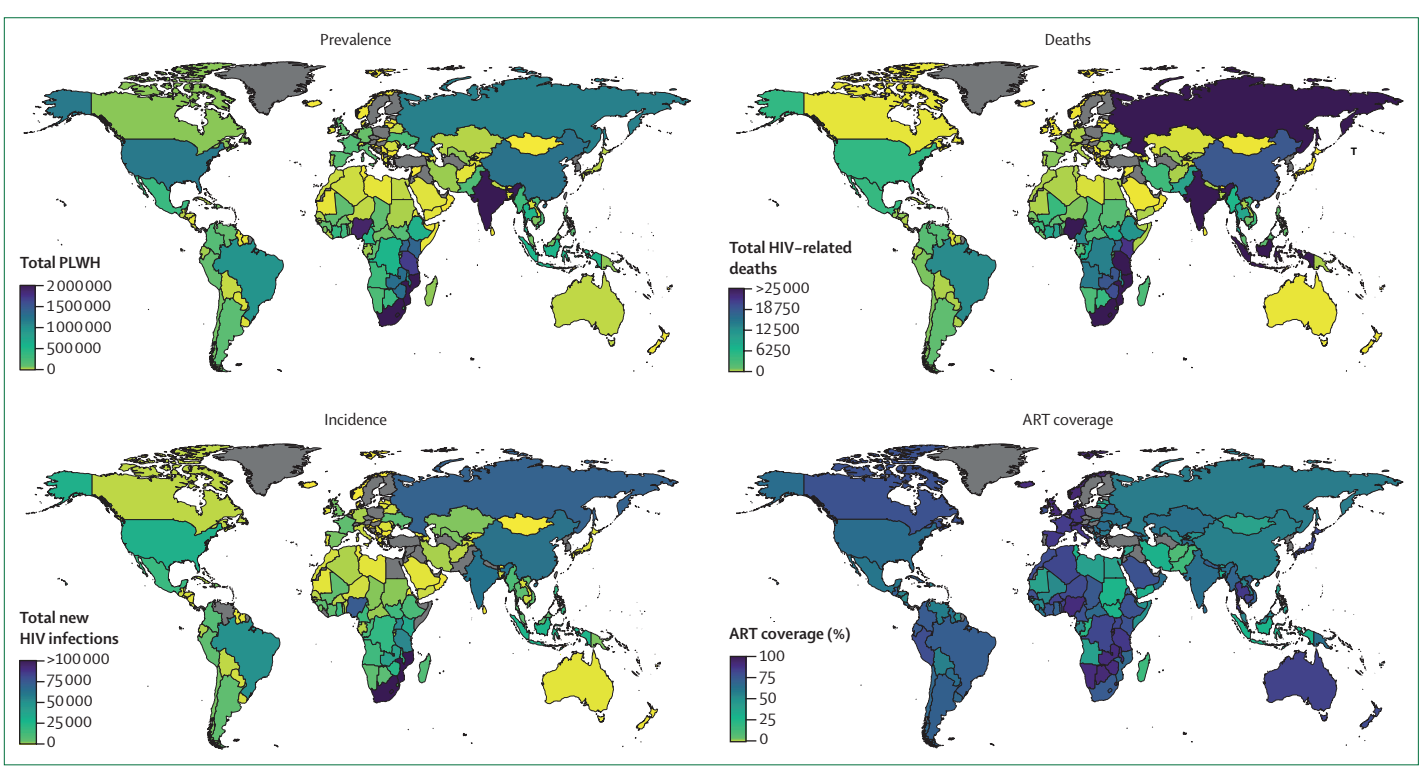

Figure 1: **Estimated numbers of people living with HIV, HIV-related deaths, new HIV infections, and antiretroviral therapy coverage**
Country data were consolidated from UNAIDS 2018 to 2021 datasets[5,6] with the most recent data for each respective country. For countries with missing data, we calculated estimates with other available indicators (eg, incidence rate and total population to estimate new infections) or sourced estimates from the respective country's government data (eg, Canada,[7] China,[8] Japan,[9] Russia,[10] UK,[11] and the USA).[12,13] ART=antiretroviral therapy. PLWH=people living with HIV.

on track.[15] On the prevention side, 144 countries had adopted WHO recommendations to offer oral HIV pre-exposure prophylaxis (PrEP) to people with substantial risk of HIV infection in 2021, and by 2022 2·5 million people had received oral PrEP at least once—more than triple the number in 2020—with most of the gains seen in eastern and southern Africa.[1] UNAIDS estimates that the global HIV treatment response has saved over 80 million life years to date, and there is additional evidence that it has also led to downstream improvements in socioeconomic prosperity and wellbeing.[16,17]

Disparities continue to drive the epidemic

Heterogeneity in epidemic severity and trajectory is holding back progress. Geographically, stark disparities are apparent (but variable) across different metrics, not only across regions and countries (figure 2), but also at subnational, district, and even neighbourhood levels.[1] In the Rakai region of Uganda, HIV prevalence ranges from 9% to 43% across small geographical areas.[18] In the USA, southern states account for 51% of new HIV infections and only 26% of PrEP users despite representing only 38% of the overall population; a majority of this excess burden is concentrated among Black sexual minority men (SMM).[19]

Even within geographical areas, HIV varies between groups defined by age, sex, gender identity, income, and race. Globally, 70% of new infections occur among key populations—defined as including people who sell sex, people who inject drugs, sexual minority men,

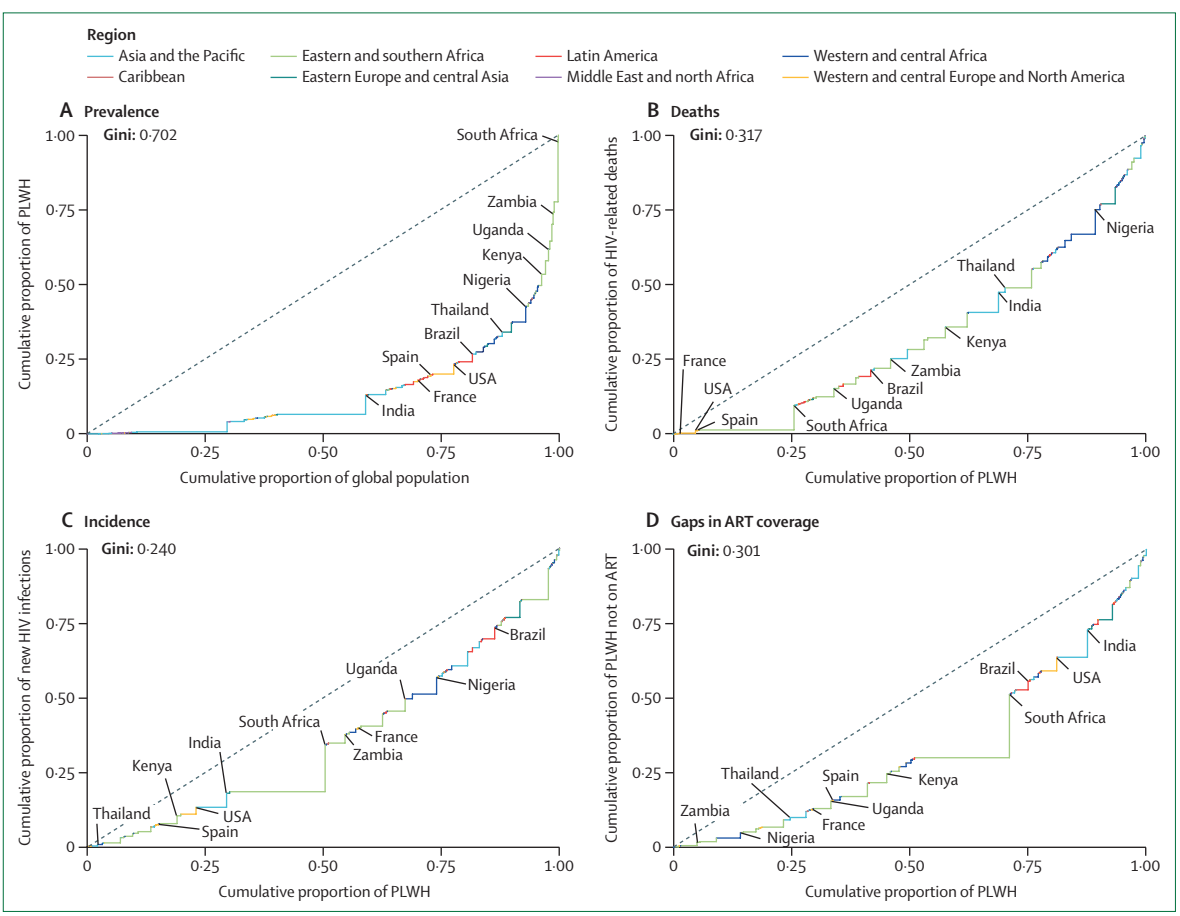

Figure 2: **Lorenz curves of disparities in prevalence, mortality, incidence, and gaps in antiretroviral therapy coverage across countries**
This figure shows modified Lorenz curves examining disparities in HIV outcomes and service delivery. Each line segment represents a country colour-coded by region that is sorted by the slope of the connecting line, with countries performing better relative to each metric sorted to the left of the each figure and countries doing worse sorted to the right. Country labels correspond to line segments immediately before the label. The dashed line represents equitable distribution if HIV prevalence, mortality, incidence, or ART coverage was evenly distributed across countries. For example, equitable distribution would occur if 50% of morbidity and mortality occurred in countries accounting for 50% of the population. The further the Lorenz curve moves from the line of equity, the more disparities there are across countries. The Lorenz curves measure disparities in the distribution of (A) prevalence (PLWH relative to the overall population), (B) mortality (HIV-related deaths relative to PLWH), (C) incidence (new HIV infections relative to PLWH [ie, slope equals the incidence to prevalence ratio]), and (D) gaps in ART Coverage (PLWH not on ART relative to PLWH). Gini coefficients are a measure of equality or inequality, with 0 indicating perfect equality and 1 indicating perfect inequality (ie, all morbidity or mortality concentrated in a single country). Country data were consolidated from UNAIDS 2018 to 2021 datasets[5,6] with the most recent data for each respective country. For countries with missing data, we calculated estimates from other available indicators (eg, incidence rate and total population to estimate new infections) or sourced estimates from the respective country's government data (eg, Canada,[7] China,[8] Japan,[9] Russia,[10] UK,[11] and the USA),[12,13] to the extent possible. ART=antiretroviral therapy. PLWH=people living with HIV.

transgender and gender diverse people, people living in prisons—and their sex partners, despite only making up 5% of the overall population, based on UNAIDS estimates.[1] These disparities are driven by the excess vulnerabilities and risks associated with stigmatising people and often hostile social and legal environments. Even as overall incidence falls, women—particularly those in susceptible age groups, minoritised, or low income—bear a greater burden of new HIV infections compared with men. In sub-Saharan Africa, adolescent girls and young women represent four of five new infections among young people now, up from three of five in 2017.[1,20,21] Once living with HIV, however, outcomes among men are 5% to 10% worse compared with women across every step of the care cascade.[1] Care continuum outcomes and incidence are substantially worse among migrants and other mobile populations.[22–24] Children younger than 14 years are tested, initiated on treatment, and virally suppressed at approximately 35% lower rates compared with those older than 15 years.[1,21,25] Across the globe, systemic inequities—such as socioeconomic and wealth disparities, racism, histories of colonialism, stigma, legal discrimination and punitive laws, and gender inequity and violence—continue to drive the HIV epidemic (figure 3).[1,15,26,27] Equitable access to prevention and treatment services across all populations will be needed to continue progress.

Using longitudinal person-centred metrics to identify gaps in care

Cross-sectional metrics, such as UNAIDS 95-95-95 helped to mobilise action, but might not be adequate in the future for identifying gaps in progress. Simulations show that improvement in these metrics can be driven simply by care programmes becoming enriched primarily for PLWH who do well on treatment and remain in care for longer periods of time. However, PLWH not adequately engaged in services or who die end up being removed from population denominators and are not accounted for.[28] Thus, these metrics can continue to improve despite the fact that person-centred longitudinal outcomes stagnate or even worsen in some populations (eg, key populations).[28]

Longitudinal assessments of individual care journeys and treatment outcomes over time paint a less sanguine picture of progress. Among new ART starters, cumulative mortality in the first 2 years is estimated to be as high as 10% in many African countries.[25,29–31] Sustained viral suppression at the individual and population levels is needed to prevent morbidity, mortality, and onward transmission, but frequent treatment interruptions and transitions in and out of care over time represent major ongoing challenges to achieving this goal, and are driven by diverse barriers[32–35] (figure 3). Even in the context of universal treatment, approximately 60% of PLWH presenting with advanced HIV disease previous to 2020 had been previously initiated on treatment, reflecting our failure to keep people engaged in care; this number has likely continued to increase in subsequent years.[36,37] Similar challenges with long-term engagement and persistence are observed in PrEP programmes as well.[38,39] Moving forward, longitundinal epidemiological assessments that centre individuals' care journeys are needed and recommended by WHO to shine light on the care gaps that will still need to be addressed.[40]

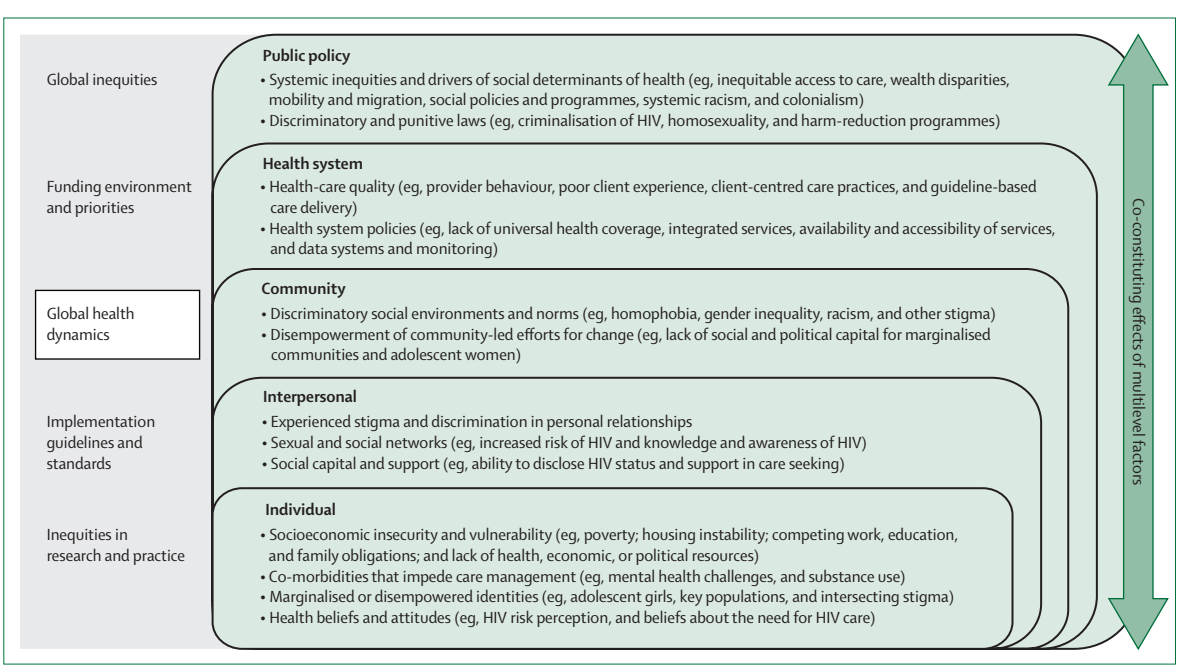

Figure 3: **Socioecological model of drivers of equitable access, implementation, and outcomes for HIV treatment and prevention**

Attending to comorbidities

Looking to the future, several important epidemiological trends will demand increased attention. Tuberculosis still remains the leading cause of mortality among PLWH and sexually transmitted infections are on the rise.[1] Increases in life expectancy with treatment is resulting in an ageing population of PLWH: the proportion older than age 50 years ranges from 17% in southern Africa to 50% in North America and Europe.[41] With an ageing population of PLWH also comes an increasing burden of NCDs including hypertension, diabetes, obesity, cardiovascular disease, cancer, and neurocognitive diseases.[42–47] Even if suppressed, PLWH have a 50% higher risk of cardiovascular mortality compared with people without HIV and that risk grows to 350% in PLWH who are not suppressed.[48] PLWH also have increased incidence and mortality from non-AIDS defining cancers, such as anal cancer, lung cancer, liver cancer, Hodgkin lymphoma, and melanoma.[49] Implementing comprehensive and integrated health services for PLWH will need to occur in parallel, with continuing efforts to successfully end the HIV epidemic.

HIV prevention

Maximising population-level effects of primary prevention of HIV infection will not be achieved by using a single modality. Access to combinations of existing (eg, oral PrEP, condoms, vaginal ring, and voluntary male medical circumcision) and emerging (eg, depot formulations) biomedical prevention technologies (table 1) and access to behavioural and harm-reduction interventions will be crucial to meet the diverse range of individual needs and preferences. In addition, prevention is best viewed with a multilevel framework whereby bio-behavioural interventions are nested within societal context, human rights, education, and poverty (figure 3), and clinicians should be attuned to these important considerations to maximise opportunities for prevention.

Treatment as prevention

Treatment as prevention remains a pillar of HIV prevention strategies. In 2011, HIV Prevention Trial Network (HPTN) 052 found that immediate treatment reduced transmission by 96% compared with treatment on the basis of clinical guidelines among 1763 serodiscordant couples in Uganda.[112] Subsequently, observational data in both serodiscordant heterosexual and SMM couples (PARTNER, PARTNER2, and Opposites Attract studies), which reported on more than 100 000 instances of unprotected sex combined, found no transmissions when HIV-1 RNA were undetectable at levels below 200 copies per mL.[113–115] IMPAACT 2010/VESTED and DolPHIN-2 studies showed that maternal viral suppression also prevents vertical transmission, with lifelong maternal ART now being the cornerstone of strategies for perinatal prevention.[80,81] In 2016, the public Prevention Access Campaign launched a campaign to promote these findings that clearly prove that "undetectable=untransmittable",[116] or U=U, which was also endorsed by WHO in 2020 to advance treatment as an HIV prevention strategy.

Although highly efficacious at the individual level, the population-level effects of implementing universal testing and treatment to prevent new infections can be highly variable across contexts. For example, robust testing is essential for first establishing HIV diagnoses before treatment can be initiated. Several large community randomised trials in Africa (eg, SEARCH, PopART, and Ya Tsie) assessing universal test and treat and other prevention interventions, showed approximately 20–30% declines in incidence, although these were not always statistically significant.[117] The seemingly disparate results from these studies can partly be explained by study design and universal treatment being offered in control communities after changes to WHO guidelines in 2016. Moreover, the studies also emphasised that the effects are highly dependent on community characteristics and heterogeneities in risk, access to care and testing, and behaviours of the unreached group, and can vary even with similar improvements in the HIV care cascade.[118] In PopART, communities that achieved similar treatment coverage (approximately 65–75%) still saw incidence rates that varied six-fold, between 0·4 to 2·4 cases per 100 person-years.[119] At present, many African countries have achieved rapid expansion of HIV testing and treatment coverage, although many gaps remain, and these findings underscore that testing and treatment is a key, but not the only component for prevention strategies.

Pre-exposure prophylaxis

Trials have shown that daily oral PrEP with either tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or tenofovir alafenamide/emtricitabine (TAF/FTC) to be nearly 100% effective at preventing HIV acquisition in diverse populations (eg, SMM, women, and people who use drugs).[53–61,120] Later studies showed that event-driven dosing is effective in preventing HIV acquisition in SMM populations (where an individual takes two pills at least 2 h before sex and then a daily pill for the next 2 days),[62,120] although data for this approach are missing among females. Outside of trial settings, the EPIC–NSW study in Australia showed the effectiveness of rolling out oral PrEP in reducing HIV incidence at the population level by 25%.[121] Scale-up of oral PrEP across the globe, however, has proven disappointing, as there are challenges with both supply (accessing health care, pharmacy refills, and provider-related barriers as bottlenecks) and demand (negatively affected by social norms, stigma, and risk perception among potential users).[57,58,122–124] Multipurpose prevention technologies (MPTs) for women that combine PrEP and contraception might be a viable solution that can help avoid stigma and unwanted disclosure.[68]

There is considerable excitement for several new technologies that have become available in the last

2 years. Long-acting injectable cabotegravir (LA–CAB)—the first long-acting systemic PrEP product—was evaluated in HPTN 083 among HIV-negative SMM and transgender women, and in HPTN 084 among heterosexual women in Africa.[63,64] Both studies showed that LA–CAB administered intramuscularly once every

	Example drugs	Clinical evidence	Clinical and implementation considerations
Prevention			
VMMC	..	Rakai,[50] ANRS 1265,[51] and Kisumu[52]	Permanent but partial protection; one-time procedure allows for novel strategies to reach populations (eg, community-based strategies); and consider preference for circumcisions
Daily oral PrEP	TDF/FTC	iPrex,[53] Partners PrEP,[54] Botswana TDF2,[55] Bangkok TDF,[56] FemPrEP,[57] VOICE,[58] iPrex OLE,[59] and PROUD[60]	Requires daily adherence and ongoing engagement in care; at least 4 doses per week might offer sufficient protection for receptive anal sex, and daily recommended for vaginal sex; cost and comorbidities can drive choice: TDF/FTC renal and bone side-effects, TAF/FTC weight gain and increased lipids; no evidence for TAF/FTC in females; and novel care models might be used to help overcome structural, psychosocial, and clinic-based barriers to long-term engagement in care
	TAF/FTC	Discover[61]	Same as above
Event-driven oral PrEP	TDF/FTC	Ipergay[62]	Essential to be able to plan to take pills at least 2 hours in advance of sex; might be preferable for some patients who have sex infrequently; requires ongoing engagement in care; evidence only among SMM and transgender women; and no evidence for event-driven oral PrEP in females
Long-acting PrEP formulations	CAB injection every 2 months	HPTN 083[63] and HPTN 084[64]	Does not require daily adherence; concerns for transmissions and resistance with long tail after missed injections; client should receive daily oral PrEP after discontinuation; viral load recommended for monitoring and considerations to align injections with lab monitoring; preferable for some clients, others might not desire due to frequency of visits to clinic or injection site reactions (depending on formulation and duration); and cost, cold-chain, and injection administration logistics remain challenges
	Lenacapavir injection every 6 months	Purpose 1 and 2 (ongoing trials NCT04994509 and NCT04925752)	Same as above
	Islatravir as monthly or yearly implant	No longer being developed due to declines in total lymphocyte and CD4 T-cell counts	Same as above
Vaginal ring	Dapivirine	RING[65] and ASPIRE[66]	Decreased efficacy in trials possibly due to adherence; might be preferable for some patients; primary roll-out focused in Africa; and no longer under consideration in the USA
Vaginal or rectal microbicide	TDF gel	Vaginal TDF gels[58,67] and rectal formulation in development	No currently approved products due to a lack of efficacy observed in trials (adherence-related)
Multi-prevention technologies	Dual prevention pill (TDF/FTC + oral contraceptive)	In development[68]	Might be more preferable for some patients; and decreased stigma associated with using a combination product
Monoclonal antibody	VRC01 monoclonal antibody every 2 months	AMP trials[69]	Proof of concept that appropriately matched bNAbs might offer longer durations of protection (27% effect overall, but 75% effective for VRC01-sensitive viruses); and should consider cost and logistics for infusion if further developed
HIV vaccine	..	RV144[70] 31.2% efficacy; VAX003[71] and VAX004[72] no efficacy; HVTN502,[73] HVTN503,[74] and HVTN505[75] no efficacy; Uhambo (HVTN 702) no effect,[76] stopped February 2020; Imbokodo (HVTN 705) no effect, stopped August 2021; Mosaico (HVTN 706) no effect, stopped January 2023; and PrEPVacc ongoing	No effective vaccines to date
Treatment			
Daily three-drug oral tablets	DTG or BIC combined with TXF (TDF or TAF) + XTC (FTC or 3TC)	First line: SINGLE,[77] ADVANCE,[78] NAMSAL,[79] VESTED,[80] DOLPHIN2,[81] ODYSSEY,[82] FLAMINGO,[83] ARIA,[84] and SPRING-2;[85] Bictegravir studies;[86-89] second line: NADIA,[90] D2EFT,[91] DAWNING,[92] SAILING,[93] and VIKING[94]	Safe and effective with high barrier to resistance, including during pregnancy; effective as second-line regimen even with non-active NRTIs, but risk of INSTI resistance in small proportion who are unresponsive to treatment (compared with PI-based regimen); INSTIs associated with weight gain, particularly in combination with TAF; requires daily adherence and ongoing engagement in care; and novel care models might be used to help overcome structural, psychosocial, and clinic-based barriers to long-term engagement in care
	DOR combined with TDF + FTC	DRIVE-AHEAD,[95] DRIVE-FORWARD,[96] and DRIVE-SHIFT[97]	Lower barrier to resistance with DOR; not co-formulated with TAF (exposure to TDF-associated bone and renal side-effects); and might be a good option for INSTI +/- TAF associated weight gain
	DRV/c or DRV/r combined with TXF (TDF or TAF) + XTC (FTC or 3TC)	NADIA,[90] DRV meta-analysis,[98] and Flamingo[83]	Consider use with adherence challenges and drug resistance; effective as second-line regimen even with non-active NRTIs; limited risk of developing PI resistance in small proportion who are unresponsive; and decreased tolerability and drug interactions with PI-based regimen

(Table 1 continues on next page)

	Example drugs	Clinical evidence	Clinical and implementation considerations
(Continued from previous page)			
Daily two-drug regimens	DTG/RPV	SWORD-1 and SWORD-2[99]	DTG/RPV and DTG/3TC not inferior to three-drug regimen, but more INSTI resistance among those who do not respond to treatment; potentially fewer long-term side-effects with NRTI-sparing regimen; and DTG/DRV/r highly effective for second-line therapy
	DTG/3TC	GEMINI-1 and GEMINI-2,[100] TANGO,[101] and SALSA[102]	Same as above
	Islatravir/Doravirine daily	ILLUMINATE studies[103,104]	Same as above
	DTG/DRV/r	D2EFT[91]	Same as above
Long-acting formulations	CAB/RPV injectable every 2 months	FLAIR[105] and ATLAS[106]	Does not require daily adherence; might be important option for patients with adherence challenges; concerns for resistance with CAB/RPV (including to INSTI) with long tail after missed injections, lower barrier to resistance, and missed previous NNRTI resistance; elevated BMI (≥30 kg/m2) and HIV-1 subtype A6/A1 also associated with increased risk of failure and resistance; preferable for some clients, others might not prefer due to frequency of visits to clinic or injection site reactions (depending on formulation and duration); full regimen (not just single medication) should be long-acting to achieve maximum benefits (CAB/RPV currently only full regimen available); considerations to align injections with laboratory monitoring and clinical visits; and cost, cold-chain, and injection administration logistics remain challenges
	Lenacapavir injection every 6 months	CALIBRATE[107] (ongoing)	Same as above
	Islatravir/lenacapavir oral weekly	Phase 2 study ongoing (NCT05052996)	Same as above
Medications for salvage therapy in heavily treatment-experienced patients	Fostemsavir oral daily	BRIGHTE[108]	Consider ease of administration, adherence concerns, other active ART, and patient preference when selecting
	Ibalizumab infusion every 2 weeks	TMB-301[109]	Same as above
	Lenacapavir injection every 6 months	CAPELLA[110]	Same as above
bNab combination	bNAb combination infusion	Sneller et al[111]	Proof of concept that passive infusion bNAbs with long half-lives can maintain viral suppression for sensitive isolates (up to 6 months); and should consider cost and logistics for infusion if further developed

3TC=lamivudine. ART=antiretroviral therapy. bNab=broadly neutralising antibody. BIC=bictegravir. CAB=cabotegravir. DOR=doravirine. DRV=darunavir. DRV/c=darunavir/cobicistat. DRV/r=darunavir/ritonavir. DTG=dolutegravir. FTC=emtricitabine. INSTI=integrase strand transfer inhibitor. SMM=sexual minority men. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. PrEP=pre-exposure prophylaxis. RPV=rilpivirine. TAF=tenofovir alafenamide. TDF=tenofovir disoproxil fumarate. TXF=TAF or TDF. VMMC=voluntary medical male circumcision. XTC=lamivudine or emtricitabine.

Table 1: **Evidence-based interventions for HIV prevention and treatment**

2 months was significantly more effective than daily oral TDF/FTC in preventing HIV acquisition, although differences might have been driven primarily by adherence. A voluntary licensing agreement established with the Medicines Patent Pool in July 2022, will allow generic access in 90 countries. Despite the enthusiasm, challenges still remain, including the frequency of visits for injections, persistence of sub-therapeutic drug levels after discontinuation (ie, pharmacokinetic tail) that requires interim coverage with oral PrEP, difficulties with identifying breakthrough infections, associated risk of integrase strand transfer inhibitor (INSTI) resistance with breakthrough infections, injection site reactions, and implementation challenges with drug storage, administering injections, and access and availability to medications in many regions of the world.[125–127] The dapivirine intravaginal ring—a flexible silicone ring that releases the non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine over a month—showed a 30% reduction in a woman's risk of HIV acquisition in the context of low levels of adherence, and up to 75% to 91% reduction when used consistently.[65,66] Adherence has been a major challenge to the effectiveness of intravaginal ring use, which may be affected by stigma and lack of acceptability among some users and emphasises the need for multiple options and choices. Dapivirine was approved in South Africa in March 2022 (followed by approvals in Zimbabwe, Kenya, Uganda, and Rwanda), but failed to garner approval in the USA.

Several other potentially game-changing prevention technologies have not yet reached commercial markets, but are being studied in ongoing clinical trials. Lenacapavir is a first-in-class capsid inhibitor that can be administered via twice yearly injections and is under investigation for PrEP in two phase 3 trials—PURPOSE 1 and PURPOSE 2. Islatravir is a first-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI) that was being evaluated for prevention and treatment as

a monthly oral drug and as an annual subcutaneous implant.[128] Studies were put on clinical hold due to reports of a dose-dependent decline in total lymphocyte and CD4 T-cell counts and the drug will no longer be developed for use in prevention. Efforts to develop additional long-acting drugs and delivery modalities continue to advance including implant formulations and prodrugs with enhanced potency, half-life, stability, and bioavailability and might become available within the next few years.[129]

Treatment

The evolution of HIV treatment has been one of medicine's unequivocal but quiet successes, as PLWH with sustained viral suppression have life expectancies approaching that of the general population. Compared with the first generations of medications (eg, zidovudine and stavudine), current treatments are associated with far fewer side-effects, dosed daily, robust against drug resistance, and can still be effective even with imperfect adherence, with long-acting treatment options on the horizon (table 1).[130]

Integrase inhibitors: the current backbone for treatment regimens

Universal treatment for all PLWH, preferably initiated on the day of diagnosis or as soon as feasible, has been recommended in WHO guidelines since 2016 on the basis of accumulating evidence, most convincingly from the START and TEMPRANO studies,[131,132] but was adopted even earlier in some countries (eg, 2012 in the USA). INSTI-based regimens with either dolutegravir or bictegravir, are now the mainstay of first-line HIV regimens due to their superiority, tolerability, and high barrier to resistance compared with NNRTI-based, boosted protease inhibitor-based, or other INSTI-based (eg, raltegravir) regimens in clinical trials including during pregnancy, in children, and with tuberculosis (for dolutegravir; table 1).[77–94] Dolutegravir was recommended for use in first-line regimens in 2014 in the USA and adopted globally in WHO Guidelines in 2018. First-line, three-drug INSTI-based regimens typically include two nucleoside reverse transcriptase inhibitors (NRTIs; usually a tenofovir prodrug [TDF or TAF] and a cytosine analogue [lamivudine or emtricitabine]). Due to its potency, dolutegravir has also been used in two-drug first-line regimens (combined with either rilpivirine or lamivudine) and they have shown no inferiority to three-drug regimens, although there was increased risk of INSTI mutations in the small percentage of PLWH who do develop treatment unresponsiveness.[99–102] There is low but increasing availability of paediatric formulations as evidence for dolutegravir-based regimens accumulates among infants and young children.[82]

As a large proportion of PLWH transition to first-line INSTI-based regimens, approaches to treatment failure and second-line regimens continue to evolve. Currently, INSTI resistance is rare[133] although NRTI resistance still occurs and INSTI resistance might grow. Among the PLWH failing first-line NNRTI-based regimens, the NADIA study—conducted in Uganda, Kenya, and Zimbabwe—showed high levels of success (>90%) and comparable outcomes between dolutegravir-based and ritonavir-boosted darunavir-based second-line regimens, even when combined with NRTIs with no predicted activity due to resistance.[90] TDF was also superior to zidovudine in second-line regimens even in the presence of predicted TDF resistance and zidovudine activity.[90] These findings add to growing evidence demonstrating that NRTIs continue to contribute to clinical success even in the presence of genotypic resistance mutations.[90,134,135] However, it is important to note that in the small percentage of PLWH who developed treatment failure in NADIA, there was a small but increased risk of dolutegravir mutations with none in the darunavir arm.[90] Moreover, recent results from D^{2}EFT suggest that a combination of dolutegravir and ritonavir-boosted darunavir can be better than a strategy of recycling NRTIs.[91] These studies show the robustness of dolutegravir and darunavir-based regimens in second-line therapy and the restricted use of genotype resistance testing to guide management for first-line treatment failure.[136] Nonetheless, optimisation to current approaches might be needed with universal use of INSTI-based first-line regimens and increasing use of LA–CAB for PrEP on the horizon, as current data were generated when NNRTI-based regimens were still the preferred first-line treatment.

Although INSTI-based regimens have shown remarkable safety and efficacy, emerging evidence has highlighted the potential for increased metabolic side-effects with these regimens. Although the mechanism is still unclear, both INSTIs and TAF have shown associations with weight gain,[78,79] although emerging evidence suggests that weight suppression from previous drugs (eg, TDF and efavirenz) might actually be the key reason.[137] Additionally, recent studies have raised the possibility of greater incidence of diabetes, hypertension, and cardiovascular events on INSTIs.[138–140] High-income country guidelines initially favoured TAF due to fewer effects on renal tubular markers and bone density compared with TDF, but WHO has retained TDF as the preferred treatment due to these weight and lipid profile concerns, and due to cost. As new evidence emerges, these concerns might lead to minor shifts in treatment guidelines, particularly for PLWH with or at risk of comorbidities, but INSTI-based regimens are still likely to be a mainstay of treatment given their robust evidence across a wide range of populations.

Future treatment horizons with long-acting formulations

The advent of long-acting formulations holds considerable promise, particularly for PLWH who struggle with adherence, but the portfolio of such regimens is only in

its infancy. An injectable combination of cabotegravir (INSTI) and rilpivirine (NNRTI) every 2 months has recently been approved for individuals who are already virally suppressed and without known resistance.[105,106] However, recent studies in unsuppressed PLWH with unstable housing and substance use have also shown effectiveness, suggesting the real public health role for long-acting formulations might be in populations that struggle with adherence.[141] Implementation challenges are similar to those with LA–CAB, particularly the development of resistance due to missed injections, a long pharmacologic tail, inadequate drug distribution with an elevated BMI, lower barrier to resistance, or previous NNRTI resistance.[126]

Several other long-acting formulations (including oral, injectable, and implantable formulations) with weekly, 2-monthly, 6-monthly, and longer dosing frequencies are currently being developed with existing and new classes of antiretrovirals.[142,143] Lenacapavir is injected every 6 months and currently approved for treatment of drug-resistant virus.[110] Studies are underway for treatment-naive individuals, but as part of regimens that contain daily oral components.[107] Oral lenacapavir combined with islatravir is also being assessed as a once-weekly regimen. A barrier to developing full long-acting regimens is the restricted partnering between commercial companies to pair appropriate existing components together, leading to delays in availability and access of effective combinations of existing drugs. There is growing excitement as studies of long-acting formulations unfold,[142] but they will not be a solution for all individuals.

Late presentations and advanced HIV remain ongoing challenges

Despite scale-up of testing and treatment, approximately 10–30% of people still present with advanced HIV (ie, with a CD4 cell count of less than 200 cells per mm³)—reflecting delays in testing and diagnosis—and are at high risk of mortality after initiating ART.[144] In addition to the need to maximise opportunities along with access to earlier testing and diagnosis, in 2017, WHO recommended a comprehensive package of diagnostic screening, treatment, and prophylaxis for advanced HIV to prevent the most common causes of death (ie, tuberculosis, cryptococcus, and severe bacterial infections).[144–149] The most prominent of these packages was outlined in the REALITY trial, which showed that a package of enhanced antimicrobial prophylaxis (continuous co-trimoxazole, 12 weeks of isoniazid–pyridoxine and fluconazole, 5 days of azithromycin, and a single dose of albendazole) reduced mortality from 12·2% to 8·9% at 12 weeks in 1805 PLWH with CD4 counts less than 100 cells per mm³ in Kenya, Malawi, Uganda, and Zimbabwe.[145] However, actual implementation has been slow and further hindered due to declines in routine CD4 monitoring at diagnosis after adoption of universal treatment guidelines and prioritisation of routine viral load monitoring.[150]

HIV pathogenesis and cure

Research on HIV pathogenesis continues to inform the development of biomedical interventions to prevent and treat infection and strategies for cure. Early in infection, HIV proviral genomes become integrated into host chromosomes and are established into viral reservoirs. Most of the reservoir is in areas of the genome that are silent and do not replicate; therefore, is not destroyed by immune surveillance.[151,152] However, a small amount of provirus can integrate into more active areas of the genome.[151,152] In the absence of treatment, these active proviruses will continue to replicate and this leads to progressive declines in CD4 T cells. CD4 T-cell depletion is exacerbated by chronic inflammation that activates CD4 T cells and can lead to fibrosis of lymphoid tissues.[153] After ART initiation, viral decay in the peripheral circulation rapidly occurs and proviral reservoirs in transcriptionally active regions also slowly decay over time, which leaves much of the reservoir in quiescent areas of the genome. However, these latently infected cells—particularly resting memory CD4 T cells—can become reactivated and cause viral rebound within days to weeks after ART discontinuation, even after extended periods of treatment.[154]

Multiple approaches are being examined for their potential to achieve a cure or remission of HIV in the absence of ART, although success might require combinations of several approaches.[2] One group of strategies seeks to reduce the size of the replication-complement reservoir by (1) stimulating it to reverse latency so that the active virus can be targeted (known as shock and kill),[155–157] (2) permanently silencing transcription of integrated provirus with epigenetic changes (known as block and lock),[158–160] and (3) using CRISPR-based gene editing to excise large regions of integrated provirus.[161] Other strategies seek to enhance the immune system to induce long-standing control of the reservoir using vaccines, broadly neutralising antibodies (bNAbs), chimeric antigen receptor T cells (CAR-T), or gene therapy.[124,162–165] A third group of strategies focuses on genetically modifying CD4 T cells so that they are resistant to HIV infection. To date, the only successful HIV cures are from this last approach by using stem-cell transplants with donor cells with the CCR5-delta 32 double-negative mutation.[166–170] The transplants were performed to treat pre-existing cancers, however, required exposure to aggressive chemotherapy and access to advanced medical care, thus restricting the approach to PLWH who are already transplant candidates. However, parallel approaches using gene-editing of the *CCR5* gene (ex vivo or in vivo) are being developed with tools including CRISPR-Cas9 or zinc finger nucleases to prevent infection of new cells.[171,172]

Advances in treatment also continue to evolve the perspectives on what the target profiles for cure strategies need to be, and raise the bar for what kinds of HIV cure strategies would be acceptable based on

	Example studies	Potential mechanisms and effects on reach, effectiveness, adoption, implementation, or maintenance (RE-AIM)
Streamlined facility-based models		
Health service delivery and implementation process*		
Cascade target: Testing	Implementation of HIV self-testing at facilities[174-176]	Improved acceptability and uptake (adoption), numbers tested (reach), and improved efficiency (implementation and maintenance)
Cascade target: Prevention	Drop-in clinic with same-day PrEP[177]	Improved acceptability (adoption), efficiency (implementation), and increased opportunity to initiate (reach and effectiveness)
Cascade target: Treatment	Facility-based adherence clubs[178-180] and extending refill duration[181,182]	Decrease burden of receiving care (acceptability and efficacy) and increased efficiency of clinic flows (implementation)
Community-based models		
Health service delivery and implementation process*		
Cascade target: Testing	Implementing HIV testing at community health fairs[183,184]	Increased access to testing (reach new populations), increased efficiency (rapid, high-volume testing–implementation), and improved acceptability (adoption)
Cascade target: Prevention	Pharmacy-based PreP programmes[185,186]	Increased availability in community (reach and adoption) and lower barrier to access care (efficacy)
Cascade target: Treatment	Community-based ART delivery[178,179,187-190]	Decreased burden of receiving care and medications (acceptability and efficacy) and care able to reach new populations (reach)
Home-based models		
Health service delivery and implementation process*		
Cascade target: Testing	HIV testing during home visits[183,191-195]	Increased access to testing (adoption) and reach populations that do not routinely access health care
Cascade target: Prevention	Home delivery for PrEP and monitoring[196]	Lower barrier to access care (reach) and more acceptable (adoption)
Cascade target: Treatment	Home-based ART delivery[197]	Decreased burden for receiving care, increased accessibility and reach, and improved acceptability
Low barrier treatment initiation		
Health service delivery and implementation process*		
Cascade target: Prevention	Same day PrEP with drop-in clinics,[177] pharmacy,[198] or community-based models[199]	Decreased barriers to starting and increased opportunity to initiate treatment (reach) with increased acceptability (adoption)
Cascade target: Treatment	Same day ART initiation[200-203]	Decreased barriers to starting and increased opportunity to initiate treatment (reach) with increased acceptability (adoption)
Navigation and care coordination		
Health service delivery, implementation process, and capacity building and support*		
Cascade target: Prevention	Navigation for PrEP initatiation[204]	Provide support for barriers to care (efficacy), increase flexibility of care and access (reach and efficacy), and develop relationships with patients (efficacy and acceptability)
Cascade target: Treatment	Patient navigation and care coordination to promote engagement in care[205-214] and tracing and outreach to promote re-engagement[205-217]	Provide support for barriers to care (efficacy), increase flexibility of care and access (reach and efficacy), develop relationships with patients (efficacy and acceptability)
Tailored care models		
Health service delivery, implementation process, and capacity building and support*		
Cascade target: Prevention	Youth-friendly PrEP,[218] PrEP delivery with youth-specific community-based mobile clinic,[219] and integrated community-based harm-reduction programmes for people who inject drugs[220]	Increased acceptability of care delivery (adoption and efficacy) and address specific needs for population (efficacy and reach)
Cascade target: Treatment	Care models tailored to meet specific needs of youth,[221-223] individuals re-engaging back into care,[206,215,224] and drop-in clinics for individuals who experience unstable housing[225] or complex needs[226]	Increased acceptability of care delivery (adoption and efficacy) and address specific needs for population (efficacy and reach)
Telehealth or mHealth strategies		
Health service delivery, implementation process, and capacity building and support*		
Cascade target: Testing	Promoting testing using mHealth[227,228]	Increased awareness, reach, and adoption of testing
Cascade target: Prevention	PrEP delivery using telehealth[229-231] and two-way SMS messaging to promote PrEP adherence and retention[232]	Decreased burden of receiving care (reach), increased accessibility (reach and efficacy), increased acceptability, foster connection with clinic (acceptability), and provider support (efficacy)
Cascade target: Treatment	Telehealth for HIV treatment[233-235] and SMS reminders and outreach[205]	Decreased burden of receiving care (reach), increased accessibility (reach and efficacy), increased acceptability, foster connection with clinic (acceptability), provider support (efficacy), and deliver theory-backed behavioural interventions (efficacy)
Leveraging social networks		
Health service delivery and implementation process*		
Cascade target: Testing	Index testing, assisted partner services; secondary distribution of HIV self-tests through social, family,[192,236-238] and sexual networks[239-241]	Reach populations not otherwise reached by testing and increased acceptability (adoption)

(Table 2 continues on next page)

	Example studies	Potential mechanisms and effects on reach, effectiveness, adoption, implementation, or maintenance (RE-AIM)
(Continued from previous page)		
Use of non-traditional actors and providers		
Health service delivery, implementation process, and capacity building and support*		
Cascade target: Testing	HIV testing with cultural (traditional healers)[242] or religious (churches)[243,244] institutions	Increase reach to populations who do not routinely access health care (reach), leverage social capital and trust to improve acceptability and uptake (adoption), and engage new HCW cadres (implementation and maintenance)
Cascade target: Prevention	Educating religious leaders to promote voluntary medical male circumcision[245] and leveraging key populations to deliver testing and PrEP[246,247]	Increase reach to populations who do not routinely access health care (reach), leverage social capital and trust to improve acceptability and uptake (adoption), and engage new HCW cadres (implementation and maintenance)
Cascade target: Treatment	Key-population led HIV services[248] and traditional healers as adherence partners[249]	Increase reach to populations who do not routinely access health care (reach), leverage social capital and trust to improve acceptability and uptake (adoption), and engage new HCW cadres (implementation and maintenance)
Delivering care at hotspots and targeted venues		
Health service delivery and implementation process*		
Cascade target: Testing	Venue-based for key populations (female sex workers[250–252] and men who have sex with men or transgender people)[252–255] and mobile testing at hotspots[253,256]	Bring testing to areas where target populations gather (reach), increase accessibility (increase reach), and increase acceptability (adoption)
Cascade target: Prevention	PrEP delivery with community-based mobile clinic at targeted locations[219]	Bring preventive services to areas where target populations gather (reach), increase accessibility (increase reach), and increase acceptability and uptake (adoption)
Cascade target: Treatment	Roadside wellness clinics for truck drivers and sex workers[257,258]	Bring treatment services to areas where target populations gather (reach), increase accessibility (increase reach), and increase acceptability and uptake (adoption)
Integration with other services		
Health service delivery, implementation process, and capacity building and support*		
Cascade target: Testing	Integrating HIV testing with hypertension and diabetes screening,[183] primary care visits,[259] emergency room visits,[260] or key population-specific care services[261]	Increase acceptability (adoption), increase access and opportunities to test (reach), and improved efficiency (implementation and maintenance)
Cascade target: Prevention	Integrating PrEP with family planning[262,263] or antenatal and postnatal care[264] and integrated sexual health services specific to sexualised substance use or chemsex[265]	Increase acceptability (adoption), increase access and opportunities for prevention (reach), and improved efficiency (implementation and maintenance)
Cascade target: Treatment	Integrating HIV and non-communicable disease care[266,267]	Increase acceptability (adoption), increase access and opportunities for comprehensive treatment (reach), and improved efficiency (implementation and maintenance)
Incentives		
Financial arrangement*		
Cascade target: Testing	Incentives or lotteries for testing[268–270] and retesting[271]	Increase motivation for testing uptake (adoption)
Cascade target: Prevention	Incentives for linkage to prevention services[272] or PrEP adherence[273]	Increase motivation for using prevention services (adoption)
Cascade target: Treatment	Incentives for linkage to care,[272] ART initiation,[274] or retention[205,275]	Increase motivation for engaging in treatment (adoption)
Strategies to optimise systems-level implementation		
Capacity building and support, implementation process, and governance*		
Cascade target: Testing, prevention, and treatment	Community-led monitoring for best practices for care,[276,277] targeting key opinion leaders and leadership,[277,278] implementing practice champions,[277,279–281] use of audit-and-feedback or dashboards,[277,281–285] and developing networks of practice for cross-learning[286]	Increased knowledge of quality and implementation gaps (implementation), increased motivation to improve care (implementation), and facilitation of quality improvement programmes (implementation and efficacy)

ART=antiretroviral therapy. HCW=health-care workers. mHealth=mobile health. PrEP=pre-exposure prophylaxis. *Implementation strategy typologies based on those used for the Living Database of HIV Implementation Research Project.[287]

Table 2: **Public health and implementation strategies for HIV testing, prevention, and treatment**

considerations, such as risks, tolerability, monitoring, costs, and scalability.[3] The risks of using aggressive interventions (eg, chemotherapies) to eradicate viral reservoirs might make them less attractive in comparison to emerging ART delivery methods that could potentially allow for once or twice-yearly dosing (eg, via injections or implants). Nevertheless, developing a cure remains a crucial priority for PLWH, emphasising the multifaceted individual considerations, such as HIV-related stigma, daily pill taking, and concerns about onward transmission that extend beyond biomedical outcomes.

Implementation and public health strategies for testing, prevention, and treatment

Learning how to implement the remarkable toolkit of safe and effective interventions optimally and equitably during routine care delivery is now central to the clinical, scientific, and public health efforts to address the HIV epidemic.[4,173] Access to testing, prevention, and treatment

and then maintaining long-term engagement afterwards remain major hurdles. Clinicians and health systems should address the social and behavioural aspects of HIV and close these implementation gaps with innovations in the who, when, where, what, and how care is offered (table 2). In all cases, a scientific lens is needed through which we can identify the correct emerging questions and methods to address implementation and socio-behavioural challenges to accelerate progress.[4]

Location and timing of services

Shifting care delivery beyond the traditional clinic-based model can extend the reach of HIV services. Testing, prevention, and treatment services are typically centred around health facilities that pose burdens to individuals with structural (eg, transportation, travel, and competing obligations), clinic-based (eg, waiting times, privacy concerns, and unfriendly providers), or psychosocial (eg, stigma, depression, substance use, and unstable housing) barriers (figure 3).[288–293] Making contact less burdensome and also reducing its frequency has been examined for testing (community fairs,[183,184] home-based testing,[183,191–195] and non-traditional venues)[250–253] and prevention and treatment (community dispensation,[179,187–190] mobile vans,[219] home delivery,[196,197] pharmacy models,[185,186] and telehealth and mobile health).[229–231,233–235,294] Such approaches are particularly important for marginalised populations (eg, key populations).[218,250–253,257,258] Differentiated service delivery is a public health approach that is gaining traction worldwide for prevention (ie, PrEP) and treatment (ie, ART), and uses models including adherence groups, community-based medication distribution, pick-up lockers, and longer scripting intervals to reduce burdens on both health systems and clients, making care both more efficient and effective.[295–297] Thus, rather than bringing individuals to care, the focus shifts to bringing care to individuals where they are.

Integration and flexibility of services

Integration of vertical health programming is an area of ongoing global public health innovation. For example, general health screenings,[183] emergency room visits,[260] or routine clinic visits[259] are highly used health-care touch-points and are crucial opportunities to achieve timely and universal HIV testing, but providers often do not think to or have reluctance in offering or discussing testing in these settings. Integrating routine opt-out HIV testing, however, has shown effectiveness in overcoming provider inertia or reluctance and reaching those who might not independently seek out testing.[183,259,260] Similarly, same day ART[200–203] and PrEP[177,198,199] programmes can increase uptake by taking advantage of opportunities to initiate prevention and treatment when an individual first presents symptoms, and some data suggest that this might lead to small improvements in the likelihood the individual returns as well. More nascent efforts seek to integrate HIV prevention and treatment with other key services including but not limited to antenatal care,[264] family planning,[262,263] harm reduction services,[265] and NCD care.[266,267] Designing more holistic care delivery platforms is ultimately what is needed for more person-centred care and to achieve the promise of the emerging universal health-care agenda. However, this is restricted by overburdened providers and vertical funding streams.

Task sharing and role revision

Expanding the range and number of individuals who deliver care can increase the reach and quality of care. Task shifting emerged as an early example primarily to address limitations in the size of the health-care workforce by re-alignment of workforce skills with needs. Capitalising on the unique skills of non-traditional providers and their relationships and social positions can also extend the capabilities of health-care systems (eg, to increase reach and decrease stigma). For example, leveraging clients to facilitate index testing and assisted partner services, or to offer secondary distribution of HIV tests to their social and sexual networks can better reach priority populations who might not otherwise access these services.[192,236–241] Additionally, studies have found promising results by training members of key populations to lead care services for their communities;[246,248] training traditional healers to conduct HIV testing,[242] and serve as adherence support partners,[249] or engaging religious leaders to promote testing[243,244] and prevention.[245] Innovative ways to diversify the people engaged in health-care delivery in order to mobilise social capital in communities and expand reach are exciting areas of ongoing work.

Health-care responsiveness

Populations are often segmented into groups that have diverse barriers, needs, and preferences for accessing testing and receiving care; what works for some or even most will not for work all.[32,36,289,292,295,298–303] Responsiveness to these diverse needs—one of the domains of quality of care—is crucial for reaching all population segments and providing equitable and sustainable clinical care and programming. Examples of tailored and person-centred clinical and public health programmes include adolescent-friendly testing, prevention, and treatment services meant to address challenges specific to their life stage;[218,219,221–223] adaptive strategies that increase or decrease care intensity based on needs;[205,295,296] 'Welcome Back' and other services tailored to unique challenges with re-entry into care after treatment lapses;[206,215,224] or clinics with low barriers to access for individuals with unstable housing or complex needs.[225,226] Key to fostering health-care responsiveness is engaging end-users during care delivery and in the design of care programme with participatory methods, such as preference surveys,[299–303] human-centred design,[304] or crowd sourcing[305] to help ensure needs and preferences are met and drive progress.

Broader systems of care

Considerations for the effects of broader systems (eg, policy environment, health systems, and clinic processes) that shape practice are increasingly becoming integral to medical training and clinician responsibilities. Data systems that routinely capture gaps in both HIV clinical outcomes[282–284] (eg, testing, retention, and viral suppression) and implementation practices (eg, engaging community to monitor care quality and client experience)[276,277] create ongoing situational awareness of where efforts should be targeted. Coupling data systems with strategies, such as champions and practice facilitators, digital dashboards, audit and feedback, and leadership training can help drive forward efforts to strengthen implementation at a provider and organisational level.[277–281] Highly successful HIV networks of practice help ensure experiential learning, education, and strategies disseminate more broadly and rapidly (eg, CQUIN HIV Learning Network for scaling-up differentiated service delivery and Implementation Science Coordinating Initiative [ISCI] for Ending the HIV Epidemic efforts in the USA). Broader considerations also include policy and legal activism to address the punitive laws, policies, and criminalisation that continue to undermine progress against HIV, and developing interim strategies while these stigmatising policy and legal environments remain in place.[26,27,306] Pursuing these types of system-level changes holds promise to be some of the most effective and efficient pathways to public health effects at this stage in the epidemic.

Conclusion

The tremendous progress in the global HIV response has been fuelled by innovations in prevention and treatment and scale-up of HIV programmes across the globe, but have not yet been matched by similar innovations in service delivery and implementation. To sustain and expand these accomplishments, new science is needed to learn how to optimally implement the available tools in ways that achieve the greatest effect on public health. Increasing attention to the inequities within the global HIV response and the systems that create them is essential for reaching all populations and addressing new infections, morbidity, and mortality. Innovations are on the horizon, but these might fall short of aspirations without considerable attention to issues of implementation and equity from the outset. HIV providers and programmes also face an ageing population living with HIV and will need to be prepared to also face growing epidemics of NCDs, including hypertension, diabetes, obesity, cardiovascular disease, cancer, neurocognitive diseases, and other ageing-related challenges. In this next phase of the global HIV response, we should consider emerging scientific questions, develop technologies, and adapt approaches to using the tools we already have so that evidence-generation and public health efforts maximise the effect and remain relevant, useful, and focused on the evolving challenges to ending the HIV epidemic.

Contributors

AM and EHG conceptualised the manuscript. All authors conducted the literature review and prepared the initial draft. AM and RKJT performed the data analysis and visualisation for the figures. All authors revised, edited, and approved the final manuscript.

Declaration of interests

EHG receives educational grants from ViiV Healthcare outside the submitted work. AHS receives grants to her institution from ViiV Healthcare and Gilead Sciences outside the submitted work. CI has received conference support and research grants from Gilead Sciences outside the submitted work. FV receives drug donations from ViiV Healthcare, Merck, Johnson & Johnson, and Gilead Sciences for investigator-led clinical studies. FV's unit perfoms investigator-led studies with the financial support of Merck, Johnson & Johnson, and ViiV Healthcare, and is performing commercial drug studies for Merck. FV's unit performs evaluations of diagnostic devices for multiple biotech companies. Individually, FV receives honoraria for educational talks and advisory board membership for Gilead, ViiV, Mylan/Viatris, Merck, Adcock-Ingram, Aspen, Abbott, Roche, Johnson & Johnson, Sanofi, and Virology Education. AM and RKJT declare no competing interests.

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