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Roadmap for Achieving Universal Antiretroviral Treatment

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Abstract

Modern antiretroviral therapy safely, potently, and durably suppresses human immunodeficiency virus (HIV) that, if left untreated, predictably causes acquired immunodeficiency syndrome (AIDS), which has been responsible for tens of millions of deaths globally since it was described in 1981. In one of the most extraordinary medical success stories in modern times, a combination of pioneering basic science, innovative drug development, and ambitious public health programming resulted in access to lifesaving, safe drugs, taken as an oral tablet daily, for most of the world. However, substantial challenges remain in the fields of prevention, timely access to diagnosis, and treatment, especially in pediatric and adolescent patients. As HIV-positive adults age, treating their comorbidities will require understanding the course of different chronic diseases complicated by HIV-related and antiretroviral toxicities and finding potential treatments. Finally, new long-acting antiretrovirals on the horizon promise exciting new options in both the prevention and treatment fields.

INTRODUCTION

The development of antiretroviral therapies that are effective against human immunodeficiency virus (HIV), paired with the infrastructure to enable the diagnosis, monitoring, and treatment of HIV and its complications, has been one of the most remarkable success stories of public health in the last 30 years. This success, coupling sophisticated diagnosis and case finding, more potent and safer treatments, and better monitoring, may extend to a future HIV cure. Addressing each aspect of HIV diagnosis, linkage to care, and treatment, or the so-called cascade of care, was accelerated by the huge injection of financial aid by donor organizations such as the Global Fund and the US President's Emergency Plan for AIDS Relief (PEPFAR), as well as by significant domestic support in many countries. This approach ultimately allowed HIV programs to include the use of antiretrovirals across the globe (1–5). Creative approaches allowed these cascade points to be addressed in many countries, which resulted in large reductions in incident infections (6).

Modern antiretroviral therapy (ART), now available in most areas of the world, has been the bedrock of the HIV response program. After a period in which HIV treatment was well known for its complicated dosing regimens and toxicities, the newest antiretroviral therapies, almost always requiring only a single pill daily, are extremely well tolerated after the first few weeks. Remarkably, life expectancy in successfully treated HIV-positive people in many parts of the world is now approaching normal. While this is likely partly due to a channeling bias, the transition from being a universally fatal condition just 25 years ago is another marker of how rapidly HIV therapy has been transformed at both the individual and population levels.

Challenges remain, including the persistently high incidence of HIV infection in many areas due to the failure of prevention programs and the issues for health systems in retaining and supporting individuals in lifelong therapy. Some countries, from diverse parts of the world, have achieved universal access—the 90-90-90 target of 90% knowing their HIV status, 90% on treatment, and 90% virally suppressed, which modelers believe will allow for epidemic control. Indeed, the incidence of infection is dropping in most areas of the world, including in southern Africa, where the burden of disease is the highest.

In this review, we briefly discuss how modern ART has evolved around these cascade innovations and our understanding of complex areas such as viral resistance. We then address challenges to the achievement of universal health and well-being for people with HIV through reducing noncommunicable disease risks among those who are successfully ageing.

HIV DIAGNOSIS

Development of diagnostic tests for HIV infection had sensitivity hurdles to clear during the 1980s and 1990s, but the current generation of tests is reliable, widely available, and affordable, with home self-testing well established in many parts of the world (7). This expansion in self-diagnosis has helped guide recent policy discussions around the expansion of COVID-19 self-sampling and home antigen testing strategies. Current programs are well served by these HIV tests, and now focus is largely on the cost effectiveness of fourth-generation tests, which add antigen testing to antibody detection, thereby narrowing the window period during which the patient tests negative with the disease early after infection, but at increased cost.

There are other diagnostic needs in the field as well (8). One area of complexity is breakthrough HIV infections in patients who are taking pre- and postexposure prophylaxis (PrEP and PEP) (9, 10) where, in some patients, antibody and antigen responses may appear blunted, delaying test positivity, and where alternative strategies around testing may be required (11). PrEP is discussed in more detail below, but as its use is expanded, the dilemma around diagnosis poses a challenge to

large-scale public health programs that have little tolerance for complexity. Another area of active diagnostics research involves testing in the setting of HIV cure therapeutics, either full eradication of the virus or a functional cure, in which the virus remains in permanent remission without continued antiviral drug pressure (10, 12, 13). Diagnosis in these patients has become the primary challenge to test success, as withdrawal of suppressive ART is the only way to establish an actual cure, and establishing eradication of viral reservoirs in inaccessible deep tissue is currently not possible (14–16). The ability to reliably diagnose the presence of residual replication-competent virus would be of substantial benefit, as withdrawal of ART is theoretically associated with significant immune destruction in patients already exposed to immunosuppressive drugs (17). There is still a need to focus on improved assays for early infant HIV diagnosis, which is key to securing early treatment, and there are similar issues related to suppression of antibodies and low viral reservoirs after very early treatment initiation (10, 18, 19). There is additional interest in recency assays, which differentiate HIV acquired within the last 12 months from more longstanding infection, to establish hot spots for public health interventions (20).

Late diagnosis remains a programmatic issue that relates to complex social determinants of health (21). A significant minority of patients with HIV present to care with severe levels of immunosuppression, often when they are ill or hospitalized. Late diagnosis remains a public health issue everywhere HIV is common (22, 23). Even the best-performing HIV testing programs are unable to reach many of these patients or link them to care after the diagnosis of HIV has been made (24). Men are heavily overrepresented in this group, and it is likely that complex issues around denial and stigma play a role, requiring the creative implementation of research (21).

TREATMENT

Modern first-line ART almost universally consists of a combination of three antiretrovirals in a daily oral tablet, or, occasionally in high-income countries, a combination of two drugs (25–28). Some patients, having failed older regimens with lower resistance barriers and requiring medications that can overcome this resistance, are still on legacy or second- and third-line therapies, comprising multiple tablets that are more toxic and more expensive than first-line therapies. Even here, many patients have been moved successfully to these new first-line therapies that have high resistance barriers, simplifying their regimens.

Since the early 2000s, oral first-line ART combinations have consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) and a nonnucleoside reverse transcriptase inhibitor (NNRTI). This combination has been the bedrock of therapy in low-income countries (and, for most of that time, in high-income countries in similar forms), with excellent efficacy in key populations that include pregnant women and those requiring rifampin-based tuberculosis (TB) therapy (25, 29). In the last 5 years, oral therapy has globally evolved by replacing the NNRTI with a second-generation integrase inhibitor (INSTI). This change has resulted in benefits in terms of both reduced toxicity and significantly increased barrier to resistance when compared to the NNRTI class of therapies (30).

Current first-line therapy combinations vary slightly between and within high- and middle-/lower-income countries. Some tinkering is occurring with the current oral three-drug therapy by switching between or removing tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) from the combination (both are featured in almost all ART worldwide) on the basis that the renal and bone toxicity associated with these two drugs would be minimized. Two- (or one-) drug simplification regimens have traditionally been unpopular, with prior iterations failing due to inadequate potency, but the combination of dolutegravir, a second-generation INSTI, with lamivudine has been shown to be durable in clinical trials and in limited real-world use (31–33).

However, this combination, as well as other dual combinations, has not proved popular in wealthier countries, probably due to the earlier experiences with potency. TDF and TAF have potent anti–hepatitis B properties when combined with lamivudine—hepatitis B is a common coinfection with HIV in many low- and middle-income countries—offering a welcome free cotreatment without the need for screening for hepatitis B; hence, the move to dual therapy by dropping TDF or TAF, both of which add minimal additional cost or toxicity, has been met with resistance in these areas of the world (34, 35).

There are differences in renal, bone, and lipid toxicities between regimens, alternately favoring either TAF (renal/bone) or TDF (lipid), but the clinical implications of these markers are unclear and are likely to need years or even decades of follow-up to establish whether these effects result in significant end-organ disease (30, 35–38). Obesity is a major side effect of treatment for people with HIV, but it appears that changing between drugs is unlikely to significantly change the weight gain trajectory (39–42). Other side effects associated with INSTI-based regimens include neuropsychiatric and sleep issues, but these are rarely significant and usually resolve. Drug-drug interactions are relatively limited with INSTIs and NRTIs, meaning that first-line therapy is relatively simple to administer (27, 28, 43).

New Therapeutic Developments

Recently, much excitement has been generated by the promise of longer-acting HIV drugs (44, 45). HIV agents with longer durations of action have been developed in oral, injectable, and implantable formulations and as infusions. The first-generation dual-therapy treatment combinations are given as two intramuscular injections every two months and were recently licensed by the US Food and Drug Administration (FDA). Newer drugs are emerging, although two of the most promising candidates, islatravir (being explored as a long-acting oral or implantable formulation) and lenacapavir (used as a long-acting subcutaneous injection), had development difficulties due to concerns around toxicity (lymphopenia in islatravir) or manufacturing issues (glass packaging with lenacapavir) (46, 47). However, there is little doubt that these, or others in development, will make their way into use. Initial candidates have demonstrated high resistance barriers, similar to the second-generation INSTIs. Additional safety data, as well as evidence of safety in pregnancy and a better understanding of drug-drug interactions, especially with hormonal contraception, will be needed before widespread use in the public health setting (48, 49). Some of these medications lack activity against hepatitis B and cannot be used with rifampin, previously both deal-breakers for public health programs.

The introduction of these new antiretrovirals into guidelines and large global public health programs entails a series of challenges that are not part of the registration process and often mean that these medications take several years before they are available for widespread use. For example, antiretroviral originator companies overwhelmingly test medications in white males, who are usually in good socioeconomic circumstances (50). Women who become pregnant are usually immediately excluded from these studies. Safety in women and during pregnancy is often only ascertained years after a drug is registered, through pregnancy registries or observational studies, posing a challenge for sub-Saharan Africa, where women of reproductive age make up most of the HIV-positive population. Guideline committees must consider the prevalence of diseases such as hepatitis B and C and of TB, since rifampin and other drugs used to treat TB have major drug interactions with many classes of antiretrovirals. The number of these conditions is often higher in Africa and Asia when compared to North America and Europe, and hepatotoxicity is a difficult clinical complication when it occurs during antiretroviral initiation (25, 49).

Children and HIV

Another challenge to the widespread adoption of long-acting injectables is that current first-line oral daily therapy is so effective. These regimens are extremely well tolerated, have a formidable resistance barrier and an acceptable safety profile for pregnant women, can be used in TB, and are very affordable in low- and middle-income countries, with multiple generic options. Because of these factors, the bar is very high, and it may take generations of long-acting agents to replace the current daily offerings.

The field of pediatric HIV is in a curious and complex position (51). Effective therapy for pregnant women with HIV has meant that HIV-positive births are rare in well-functioning HIV programs; for instance, in South Africa, cases have dropped from a peak of 70,000 children born with HIV every year to just under 2,000 a year (52–55). This, however, creates downstream program issues. First, case finding becomes much harder, especially as pediatric HIV patients require definitive diagnosis months after birth, when they may be lost to follow-up (19). Secondly, children require dose titration as their weight changes (and switches from liquid to oral formulations, and from protease to integrase inhibitors), which requires a level of experience unavailable at most primary care facilities. Next, the lower numbers of children born with HIV means that there is no commercial impetus for pharmaceutical companies to develop new formulations, and fewer patients are available for participation in clinical trials (the FDA has recently issued alternative development guidance in recognition of this) (56). Finally, the complexity of managing children, with secondary caregivers, issues around disclosure, and transition to adolescence and subsequent impact on adherence, means that this population will need continued focus in the future. However, the benefits are profound if these complications are managed, with the first children born with HIV starting to see their grandchildren entering the world, a further testimony to the long-term efficacy of ART (57).

Treatment, Drug Sequencing, and Antiretroviral Resistance

Philosophically, modern ART has undergone a major shift in thinking in the last decade. One of the most debated research issues in the HIV field is suddenly in a peculiar pause, as the new generation of integrase inhibitors and new classes of drugs have introduced resistance barriers that have thus far proven nearly insurmountable, completely overturning previous treatment and monitoring paradigms (58–60).

Confronting antiretroviral resistance has occupied the HIV world since the development of polymerase chain reaction (PCR) technologies to measure HIV viral load and, subsequently, the development of HIV resistance genotyping (61). HIV is highly mutagenic, generating every known resistance mutation in viral progeny in untreated patients every day, meaning that non-suppressive regimens select resistant strains of HIV within the patient, with resultant viremia and continued immune dysfunction, as well as potential community spread of resistance (1, 15, 62, 63). Genotyping has been done in many high-income countries in newly diagnosed patients to guide the initial selection of ART, although data to support this approach have been lacking in recent years (15, 64). NNRTIs were used routinely in first-line therapies until the availability of INSTIs, as they were the best tolerated but had the lowest barrier to resistance and failed with resistance when adherence was even slightly compromised (65). Other drugs with more robust resistance barriers, mainly the protease inhibitor class, had more side effects, twice daily dosing, greater tablet burdens, drug-drug interactions, food restrictions, and greater metabolic toxicity, and they were often more expensive (65).

As a result, the notion of sequencing antiretrovirals has been an integral part of ART for two decades, putting the safest (but most fragile) NNRTI-based regimen up front, with tailored

offerings that include later use of the protease inhibitors (29, 65). In high-income countries, genotyping was used to guide these choices, but in most of the world, resistance selection was relatively predictable, with blind cycling based on either clinical, immunological (CD4 lymphocyte), or virological criteria that marked failure. The World Health Organization (WHO) and guideline groups used this knowledge about resistance to select best-guess regimens once failure was established, depending on the resources available. This approach, first used in WHO guidelines in 2003, involved replacing NRTIs (later maintaining lamivudine) while changing the NNRTI to a protease inhibitor, and it was very effective, with subsequent large randomized controlled trials (RCTs) confirming the approach, showing that viral suppression was possible in the large majority of cases (65–68).

These RCTs and other studies contributed data to the increasing recognition that standard genotyping algorithms did not always accurately predict responses to future regimens. This finding built on the long-standing recognition that resistance to cytosine analogs such as lamivudine conferred additional potency to partner antiretrovirals, paradoxically strengthening combinations (69). The original genotyping scoring system was built for antiretroviral monotherapy and subsequently adapted to accommodate dual and triple therapy, but validation was complex (63). These prediction scores, when applied retrospectively to samples used in these RCTs, suggested that blind sequencing should not work, as many of the drugs, specifically the NRTIs, should have no activity against HIV. In fact, almost all the patients were suppressed despite having, in theory, no functional NRTIs (66, 67). The mechanism of this residual activity of the NRTIs and the potency of the overall regimen functions are the subjects of much speculation in the resistance world, and they have led to more confidence in designing studies that recycle drugs that were previously assumed to have been lost to resistance.

Even as this resistance conundrum was playing out around recycled NRTIs, the wealthier parts of the globe saw the rapid ascent of the second-generation INSTIs, specifically dolutegravir and bictegravir, initially due to their significant tolerability benefits over NNRTIs (70). However, it became apparent that these drugs conferred remarkable barriers to resistance in all lines of therapy. Confirmed INSTI resistance has been documented in only a handful of cases despite use in tens of millions of first-line patients (71). Introduction of these drugs into legacy patients, on various second, third, and salvage regimens, has similarly meant that many have seen their virus controlled and their treatments simplified. Virological control in the INSTI era is almost routine, even in patients with significant previous treatment histories and documented resistance. However, occasional failure with these INSTIs has been documented in people previously failing older integrase inhibitors such as raltegravir (34). This is of concern with the introduction of cabotegravir, also an INSTI, but used as an injectable formulation in PrEP and treatment programs. Cabotegravir has an exceedingly long tail, which means that significant plasma levels are detectable for months or even up to a year after discontinuation and may be able to induce resistance in seroconverting patients, especially as cabotegravir has a lower resistance barrier than dolutegravir or bictegravir (44, 72, 73). Cabotegravir has only been used in prevention registration studies and only very recently in treatment studies, so use in less-monitored arenas may see more cases of resistance (74–76).

Circulating resistance has been steadily dropping in wealthier countries, and despite the almost universal use of INSTIs in some countries for nearly 10 years (including the use of first-generation INSTIs), little circulating INSTI resistance has been seen (27). In low- and middle-income countries, NNRTI resistance has been steadily rising, a by-product of NNRTI-based first-line therapy, since large-scale public health programs started in the early 2000s (77). However, this issue is likely to recede with the mass replacement in first-line and much of subsequent-line patients, with fixed dose combinations with dolutegravir replacing efavirenz-based NNRTI combinations (34, 71, 78–80). Interest is now focused on whether this transition will lead to resistance in viremic

RESEARCH THAT SHIFTED HIV PRACTICE

Arguably the most important HIV study of the last 12 years was the National Institutes of Health–funded HPTN 052 randomized control study (136). Breathtaking in its ambition, budget, scale, and geographic scope, and negotiating the roller coaster of rapidly evolving HIV guidelines, the study allocated serodiscordant couples to arms deferring antiretroviral therapy (ART) in the HIV-positive partner versus immediate initiation of treatment between 2007 and 2010. At the time, it was not recommended that people initiate ART at high CD4 counts, as therapy was toxic, benefits appeared marginal at best, and options after developing resistance were toxic. Essentially, HIV-positive people were being called on to take treatment to protect their partners. The initial report was astonishing—28 infections occurred in the deferred arm linked to their partner, and only one case occurred in the treatment arm, probably due to an undiagnosed seroconversion at study entry. The results were confirmed in subsequent follow-up, along with a modest morbidity benefit for those starting therapy. The morbidity and then mortality benefits were proven to be much larger by the subsequent highly influential START study and others once safer ART was used (144). However, the transmission benefit confirmed earlier observational studies and provided major impetus for the international treatment movement over the next decade.

patients—with accumulating information from two sources, the NADIA and ARTIST studies, that recycling of TDF and lamivudine is effective (77, 81–83).

In 2022, where does the resistance landscape stand (60, 84)? It may be less of a clinical concern, at least in the medium term, than it was in the past. Patients routinely achieve viral suppression, and if this is not so, the only plausible reason, if they are using second-generation INSTIs, is nonadherence, as opposed to previous regimens where viral resistance may have been a cause. Interventions are no less complex—adherence can be notoriously difficult to achieve—but the root cause of viremia does not require genotyping. New candidate drugs under development are unlikely to return us to the old paradigm of sequencing (84). In the process, we are seeing the steady extinction of a range (and even whole classes) of older antiretrovirals in the face of the integrase inhibitor era, including efavirenz and other NNRTIs, azidothymidine (AZT), the older integrase inhibitors, and, probably soon, all the protease inhibitors, at least for adults (pediatric HIV has a far more limited formulary) (see the sidebar titled Research that Shifted HIV Practice).

STAGING AND MONITORING OF HIV DISEASE

Initial attention focused on identifying biomarkers of disease progression, and then, as increasingly effective ART evolved, on the use of biomarkers to monitor treatment (85). The identification of the now ubiquitous CD4 count, a subset of lymphocytes that when depleted correlate well with immune suppression and risk of opportunistic illness, was a major breakthrough in the pre-ART era. The CD4 count allowed clinicians to develop differential algorithms for complex clinical presentations and for both the initiation and discontinuation of infection prophylaxis.

The next breakthrough was the development of quantitative viral load monitoring, using PCR, which initially allowed for a more nuanced understanding of HIV disease pathogenesis and transmission risk and for the impact of ART. A still widely used pathogenesis metaphor introduced by John Mellors in 1996 is a train on a track, heading for disaster, with the train being the patient, the length of track the CD4 count, and the viral load the speed of the train (86). As antiretrovirals came into development, the metaphor was adapted to include the impact on viral load (slowing the decline and eventually allowing the CD4 count to recover, reversing the train) and even nonadherence and the development of resistance. Viral load thresholds serve two purposes—they

serve as a level at which transmission occurs and at which triggers for switching occur before the accumulation of significant resistance. WHO uses 1,000 copies/mL as a compromise to balance unnecessary switching with the ongoing development of resistance; however, recent work, which was done on NNRTI-based regimens that are now being phased out, suggests significant predicative failure below this threshold (87). Viral loads remain the cornerstone of HIV therapeutic monitoring in modern guidelines, but the expense and complexity of testing mean that poorer countries still do not routinely have access to this technology. Hence, strategies to either simplify, replace, or expand testing continue to be a focus of universal roadmap strategies. In addition, the quantitative aspect of testing is being interrogated; absolute numbers at the lower thresholds of detection trigger drug switches in lower-income countries, and any levels of detectability may trigger expensive genotyping testing in richer areas. With the onset of modern INSTI regimens that, as yet, do not select for resistance in first-line treatment, it is unclear what value these thresholds serve or, indeed, whether genotyping is required at all.

The future steps in staging and monitoring are, paradoxically, how to simplify the above. As ART has become more predictably effective and immune reconstitution routine, guidelines have begun dropping the monitoring of CD4 count. There is strong interest in developing screening tests for use before doing viral load or point-of-care testing or developing complete alternatives to viral load testing. Ultimately, the goal for large public health programs, which often treat many millions of patients in the public sector, will be to develop effective differentiated models of care (88). In such models, the vast majority of patients who are doing well with virologic control can be offered long-term treatment prescriptions and few clinic visits, with resources focused on the few high-risk patients who struggle with treatment.

AGEING AND HIV

Predictably, as HIV-positive people age, they develop the complications of growing older, including a whole range of noncommunicable diseases and cancers (89, 90). On top of this, HIV and antiretrovirals play a complex and evolving (albeit controversial) role in this ageing process.

In many countries, people with HIV are drawn from communities that exhibit behaviors that put them at risk for these diseases. In many northern-hemisphere countries, HIV-positive communities have a very high prevalence of smoking and associated frailty, and in areas where needle sharing is the main route of transmission, untreated hepatitis C causes a large amount of chronic liver diseases (91). In sub-Saharan Africa, smoking and chronic lung disease as a result of treated tuberculosis are common problems (92, 93).

HIV itself, even when successfully treated with viral levels below the point of detection, appears to be associated with low-level continued inflammation. This inflammation is a concern, as it appears to be associated with long-term endothelial dysfunction and increased cardiovascular and other diseases (94–98). Large studies are currently looking at the routine use of statins in HIV-positive populations, utilizing their anti-inflammatory and lipid effects, and the results of these studies may signal a new frontier in primary prevention strategies in this patient population (99).

Since 2017, obesity has emerged as a major issue within modern ART. Debates rage as to whether specific antiretrovirals impact weight gain as either facilitators or mitigators, but it appears that weight gain may be a feature of all modern antiretroviral therapies, a major concern in a world where the obesity epidemic is emerging as the next major health challenge across the globe, especially in middle- and low-income countries (40, 41, 100–105). Few options currently exist for addressing weight gain in treatment guidelines and essential drug lists, and the few pharmaceutical agents available are rarely used (106). However, promising agents are rapidly emerging, and integrating these within HIV care, for a priority population at very high risk of new-onset obesity, is likely to be a therapeutic priority for new research (107, 108).

To make this picture even more complex, antiretrovirals may play a role, by class and even by individual drugs within classes, in metabolic outcomes (109). Older antiretrovirals have impacted metabolic outcomes as diverse as glucose, lipid, and bone metabolism. Currently used NRTIs are implicated in renal and bone changes, as discussed above, and some INSTIs can increase inflammation (94). Most HIV-positive patients live in low- and middle-income countries, and traditional risk factors such as increases in glucose, lipids, blood pressure, and weight, as well as other factors, are correlated with verified cardiovascular and other outcomes seen in rich countries. Even within the richest countries there is concern that simply applying these risk factors from HIV-negative populations may not give a true picture of future risk for HIV patients, specifically with calculators being adapted for people living with HIV (110–112).

TREATMENT STRATEGIES

Initially, patients infected with HIV were treated with antiretrovirals, given as often as every four hours, in handfuls of tablets, with many causing significant side effects, requiring doctors with significant expertise. Treatment has since evolved to the point where most patients can adequately self-manage themselves within the context of primary care, with occasional visits to a facility and obtaining annual blood draws, and physician expertise is only required as needed. While modern treatment is very well tolerated, adherence remains an issue, and social determinants have steadily become more common reasons for patients' poor adherence. Poverty, lack of access to care, mental health issues, substance use, unstable living conditions, changing employment, and a range of other factors impact adherence and often are far more complex for clinicians to solve (113–116). In much of the world, especially in rich countries such as the United States, simply having access to affordable health care is highly predictive of successful virological suppression. As discussed above, maintaining adequate adherence in adolescents is particularly difficult, resulting in far lower suppression rates than in adults or pediatric preadolescent populations.

Same-day initiation has been the most recent programmatic innovation, in which treatment is started, if patients are deemed ready, on the day an HIV diagnosis is made (117, 118). This strategy was found to be safe in randomized clinical trials using a simple screening algorithm that excluded comorbidities that could make rapid induction with ART risky. This approach resulted in a greater proportion of patients being retained in care in the medium term, with similar viral suppression between treatment arms. In countries with PEPFAR programs, this policy has been rapidly rolled out and has been largely successful, despite significant clinician discomfort around patient preparedness for this rapid induction. Other innovations in treatment strategies have focused on delivery of services, including drug delivery to localities closer to patients' homes and including multimonth prescriptions (119, 120). Patient tracking and electronic systems that capture patient details and data from pharmacy and laboratory systems have been frustratingly difficult to implement, even in rich countries, and not just for HIV management. However, efforts continue to be made to scale these systems beyond pilot projects, recognizing the enormous need for better monitoring and evaluation of these programs (121). The use of digital platforms/mHealth to maintain patient engagement and communication for retention has had mixed success globally and has been hard to achieve in most settings, largely due to data safety and security acts imposed by countries, as well as the cost of collecting and maintaining the data (122). Innovative decentralized care models using private pharmacies to initiate PrEP, PEP, and therapy are being explored in several areas of the world (123, 124).

Prophylaxis against HIV-linked opportunistic disease, both primary and secondary, as well as treatment, has largely remained the same for the last decade, except for progress in the treatment of cryptococcal meningitis, where more abbreviated and simpler forms of treatment

with amphotericin B are being tested, and the judicious use of steroids in hospitalized patients with immune reconstitution tuberculosis (28, 125–127).

HIV CURE

Utilization of stem cell techniques to introduce genetic subtypes associated with cellular immunity to HIV infection into HIV-positive patients, altering the host genome, has now been shown to be possible (62, 128–130). Ironically, HIV treatment has evolved to the extent that the strategies to effect a cure are far more toxic than current ART and can only be implemented when addressing a concomitant severe disease. As a result, only four people thus far have been cured (and most have had significant side effects) (131). However, these gene therapies and other proofs of concept provide a parallel roadmap to possible future cure strategies, and the National Institutes of Health and others have provided significant resources to encourage research in this area. Whereas many cure strategies, ranging from the use of monoclonal antibodies to HIV latency reversal, are under study, this field of research remains years away from an effective, scalable option, which reinforces the need for further strengthening HIV cascade programs and HIV prevention methods (132).

HIV PREVENTION

Any roadmap to treatment necessarily needs to include approaches to HIV prevention. Populations vulnerable to HIV vary widely between and even within geographical areas and evolve over time. Heterosexual transmission is still prominent in much of southern Africa, which contains over 70% of the global burden of disease. A significant proportion of transmission is found among young women and sex workers. In much of the rest of the world, incidence is high among men who have sex with men, injecting drug-using populations, transgender populations, and sex workers (2, 133). Overall, HIV incidence is declining globally, but this figure conceals huge complexity, with large drops in incidence in women in southern Africa, but with a large epidemic in some eastern European countries. A recent switch in the United Kingdom to heterosexual transmission of new infections is testament to how HIV epidemiology can change (134). The decline in global infection rates is complex and probably due to a combination of the natural dynamics seen with infectious diseases more generally affecting the most vulnerable initially, antiretroviral access, and behavioral factors such as access to condoms and circumcision, all of which vary markedly by area (2). A new hypertransmissable variant of HIV identified in Holland has sounded alarms, probably based on the concomitant COVID-19 epidemic and hyperawareness of variants such as Omicron, and it is uncertain whether this has any real impact on HIV transmission dynamics (135).

The recognition that full viral suppression in HIV-positive people eliminates onward transmission has further renewed the impetus for addressing increased access to ART, and the test and treat focus of the last few years has been a major thrust of donor agencies such as PEPFAR in the quest for epidemic control (136).

Existing prevention modalities, such as medical male circumcision and condoms, have recently been supplemented by PrEP, which provides high levels of protection to both men and women when taken orally. New prevention options, including a vaginal ring and injectable cabotegravir, both of which are poised to enter the market, along with other forms of oral, injectable, and implantable agents, are being explored in preregistration and registration studies (44, 137, 138). PrEP uptake has been poor outside of a few major cities and within some verticalized key population programs, but even this limited uptake has been associated with profound drops in incidence in certain countries in Europe and in cities in the United States (138, 139).

HIV vaccine and microbicide research efforts continue, although recent efforts have again been unsuccessful (137, 140). There is renewed optimism and enthusiasm for research in the vaccine

field, some related to the success of the messenger RNA vaccines and the sheer speed of clinical trial results seen during the SARS-CoV-2 pandemic.

Prevention efforts continue to be constrained in many parts of the world, as evidence-based interventions are thwarted by legal frameworks that prevent access to stigmatized populations at high risk for HIV. Harm reduction programs have been shown to work in a wide range of scenarios but are often denied to people who inject drugs, while ongoing criminalization of sex work and homosexuality in some countries hampers efforts to access certain populations (141). Different strategies to monitor the epidemic, including the use of recency assays, are challenging, especially when interventions lack precision or focus, requisite evidence of efficacy, or the resources to make a difference (142). Finding a hot spot of infections in a community is appealing to public health outbreak workers, but there are few successful models that address effective methods to intervene, other than perhaps renewed efforts to improve access to testing and antiretroviral care. Increasingly, it appears that a kitchen-sink approach—combining multimodal prevention strategies that target many different populations and individual preferences—will be the most effective prevention strategy from a public health perspective (56).

ACCESS TO MEDICINES AND INNOVATIONS

HIV medicine does offer some lessons to the rest of the medical field—with enough ambition, focus, and resources, remarkable achievements are possible, especially when everyone with a stake in the outcome, including patients and communities, is involved meaningfully in the discussions around how to make this happen (143). It is interesting to see that some of these lessons are being applied to the diagnosis and treatment of tuberculosis, for which significant gains are being made (125, 133).

HIV therapy has become the benchmark for achieving improved adherence. Older antiretroviral combinations had very little forgiveness, so adherence rates of around 90% were required, and strategies to routinely attain this were required from both clinicians and patients. Importantly, this high level of adherence was required outside of specialist clinics and at scale, even in the poorest areas of the globe. Meaningful patient buy-in was paramount and has been successful in most cases, compared with lower success rates seen in routine hypertension, diabetes, and other chronic care situations (88). However, HIV clinics have been less effective at integration of other beneficial services such as TB screening, and other screening services, such as for contraception, are almost nonexistent (116, 120). A fully integrated clinic, in which all chronic diseases and health needs are screened consistently, needs to be the new model. Whereas the PEPFAR program has become a global model of effective public health funding and implementation in response to a global epidemic, it has also reinforced our understanding that additional programs, funding, and attention to other conditions will be needed to combat the changing priorities for people with HIV. The program might also serve as a model for combatting the next generation of health priorities, such as noncommunicable diseases, which will also benefit from sustained support for chronic disease care strategies.

CONCLUSION

The road map looks promising from afar: excellent diagnostic tools, with results available in minutes, followed by same-day initiation with very safe, highly potent single daily tablets that appear to have the ability to suppress the virus for years, possibly forever, while completely blocking onward transmission, and the virus in retreat in terms of global incidence. Millions of people are alive today due to the success of the global HIV care program, and people with HIV can look

forward to living normal or near-normal life spans, with no restrictions on their ability to work, have families, play sports, or participate in society in any way.

However, as people on these antiretroviral therapies age, a whole series of new challenges are facing them, as the unknowns of chronic viral infection and its impact on other diseases associated with ageing manifest themselves. Obesity and its associated complications, a particular feature of successfully treated HIV, may prove to be one of the most difficult clinical issues to address in a world in which obesity remains a growing and poorly addressed issue. Aggressively addressing associated factors—smoking, frailty, poor diet, and substance abuse that may contribute to ill-health—is a key issue for HIV clinicians going forward.

At a public health level, continued focus on prevention and case finding, using effective but underutilized interventions such as harm-reduction interventions and PrEP, will allow for further incidence reductions. There are still populations that need more attention; pediatric HIV is rare but requires focused attention to ensure that they get the complex health care they require for good outcomes, and adolescent care is especially fraught with adherence challenges.

While cure strategies may figure in the distant future, the immediate therapeutic breakthroughs are more likely to be found in long-acting medications, accompanied by therapeutics addressing inflammatory and chronic diseases, as either primary or secondary prevention.

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LITERATURE CITED

1. Fauci AS, Lane HC. 2020. Four decades of HIV/AIDS—much accomplished, much to do. *N. Engl. J. Med.* 383(1):1–4
2. UNAIDS. 2021. AIDSinfo. UNAIDS. **https://aidsinfo.unaids.org/**
3. WHO (World Health Organ.). 2021. *HIV/AIDS*. Key Facts, WHO, Geneva, Switz.
4. UNAIDS. 2017. *Ending AIDS: progress towards the 90-90-90 targets. Global AIDS update 2017*. Rep., UNAIDS, Geneva, Switz.

5. Levi J, Raymond A, Pozniak A, Vernazza P, Kohler P, Hill A. 2016. Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades. *BMJ Glob. Health* 1(2):e000010
6. Hill A, Pozniak A. 2015. HIV treatment cascades: How can all countries reach the UNAIDS 90-90-90 target? *AIDS* 29(18):2523–25
7. Santella AJ, Majam M, Van Ngo H, Luis H. 2020. HIV testing: What, where and how? *Oral Dis.* 26(Suppl. 1):112–16
8. Facente SN, Busch MP, Grebe E, Pilcher CD, Welte A, et al. 2019. Challenges to the performance of current HIV diagnostic assays and the need for centralized specimen archives: a review of the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA) repository. *Gates Open Res.* 3:1511
9. Wagner AD, Kinuthia J, Dettinger J, Mwongeli N, Gomez L, et al. 2021. Challenges of discrepant HIV tests in pregnant women in the PrEP era-to treat or not to treat? *J. Infect. Dis.* 223(2):234–37
10. Amin O, Powers J, Bricker KM, Chahroudi A. 2021. Understanding viral and immune interplay during vertical transmission of HIV: implications for cure. *Front. Immunol.* 12:757400
11. Parker I, Khalil G, Martin A, Martin M, Vanichseni S, et al. 2021. Altered antibody responses in persons infected with HIV-1 while using preexposure prophylaxis. *AIDS Res. Hum. Retroviruses* 37(3):189–95
12. Mori L, Valente ST. 2022. Cure and long-term remission strategies. *Methods Mol. Biol.* 2407:391–428
13. Cohen J. 2022. Mapping where HIV hides suggests cure strategy. *Science* 375(6577):130–31
14. Busman-Sahay K, Starke CE, Nekorchuk MD, Estes JD. 2021. Eliminating HIV reservoirs for a cure: The issue is in the tissue. *Curr. Opin. HIV AIDS* 16(4):200–8
15. Parikh UM, McCormick K, van Zyl G, Mellors JW. 2017. Future technologies for monitoring HIV drug resistance and cure. *Curr. Opin. HIV AIDS* 12(2):182–89
16. Lambrechts L, Cole B, Rutsaert S, Trypsteen W, Vandekerckhove L. 2020. Emerging PCR-based techniques to study HIV-1 reservoir persistence. *Viruses* 12(2):149
17. Kibirige CN, Manak M, King D, Abel B, Hack H, et al. 2022. Development of a sensitive, quantitative assay with broad subtype specificity for detection of total HIV-1 nucleic acids in plasma and PBMC. *Sci. Rep.* 12(1):1550
18. Okusanya B, Kimaru LJ, Mantina N, Gerald LB, Pettygrove S, et al. 2022. Interventions to increase early infant diagnosis of HIV infection: a systematic review and meta-analysis. *PLOS ONE* 17(2):e0258863
19. Chadwick EG, Ezeanolue EE, Comm. Pediatr. AIDS, Hsu KK-C, Kourtis AP. 2020. Evaluation and management of the infant exposed to HIV in the United States. *Pediatrics* 146(5):e2020029058
20. Facente SN, Grebe E, Maher AD, Fox D, Scheer S, et al. 2022. Use of HIV recency assays for HIV incidence estimation and other surveillance use cases: systematic review. *JMIR Public Health Surveill.* 8(3):e34410
21. Lancet HIV. 2022. Time to tackle late diagnosis. *Lancet HIV* 9(3):e139
22. Lee JS, Humes E, Hogan BC, Justice AC, Klein M, Gebo K, et al. 2022. Observed CD4 counts at entry into HIV care and at antiretroviral therapy prescription by age in the USA, 2004–18: a cohort study. *Lancet HIV* 9(Suppl. 1):S2
23. Mounzer K, Brunet L, Fusco JS, McNicholl IR, Diaz Cuervo H, et al. 2022. Advanced HIV infection in treatment-naive individuals: effectiveness and persistence of recommended 3-drug regimens. *Open Forum Infect. Dis.* 9(3):ofac018
24. Mutru M, Isosomppi S, Aho I, Liitsola K, Brummer-Korvenkontio H, et al. 2022. Finnish HIV quality of care register (FINHIV). *BMJ Open* 12(1):e053287
25. Vitoria M, Rangaraj A, Ford N, Doherty M. 2019. Current and future priorities for the development of optimal HIV drugs. *Curr. Opin. HIV AIDS* 14(2):143–49
26. Ryom L, Boesecke C, Bracchi M, Ambrosioni J, Pozniak A, et al. 2018. Highlights of the 2017 European AIDS Clinical Society (EACS) Guidelines for the treatment of adult HIV-positive persons version 9.0. *HIV Med.* 19(5):309–15
27. Saag MS, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, et al. 2020. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society–USA panel. *JAMA* 324(16):1651–69
28. Nel J, Dlamini S, Meintjes G, Burton R, Black JM, et al. 2020. Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults: 2020 update. *South Afr. J. HIV Med.* 21(1):1115

29. Ford N, Ball A, Baggaley R, Vitoria M, Low-Beer D, et al. 2018. The WHO public health approach to HIV treatment and care: looking back and looking ahead. *Lancet Infect. Dis.* 18(3):e76–86
30. Venter WDF, Serenata C, Vitoria M, Mkhondwane L, Sikwese K, et al. 2021. What we have learned from antiretroviral treatment optimization efforts over the last 5 years? *AIDS* 35(Suppl. 2):S113–15
31. Dupont E, Yombi JC. 2019. Is antiretroviral two-drug regimen the new standard for HIV treatment in naive patients? *AIDS Rev.* 21(3):143–56
32. Patel R, Evitt L, Mariolis I, Di Giambenedetto S, d'Arminio Monforte A, et al. 2021. HIV treatment with the two-drug regimen dolutegravir plus lamivudine in real-world clinical practice: a systematic literature review. *Infect. Dis. Ther.* 10(4):2051–70
33. Antinori A, Santoro MM, Gagliardini R, Marchetti G, Mondi A, et al. 2019. Italian expert panel consensus statements on two-drug antiretroviral regimens to treat naive and virologically suppressed HIV-1 infected patients. *New Microbiol.* 42(2):69–80
34. Vitoria M, Hill A, Ford N, Doherty M, Clayden P, et al. 2018. The transition to dolutegravir and other new antiretrovirals in low-income and middle-income countries: What are the issues? *AIDS* 32(12):1551–61
35. Gotham D, Hill A, Pozniak AL. 2017. Candidates for inclusion in a universal antiretroviral regimen: tenofovir alafenamide. *Curr. Opin. HIV AIDS* 12(4):324–33
36. Squillace N, Ricci E, Menzaghi B, De Socio GV, Passerini S, et al. 2020. The effect of switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) on liver enzymes, glucose, and lipid profile. *Drug Des. Devel. Ther.* 14:5515–20
37. Agarwal K, Brunetto M, Seto WK, Lim Y-S, Fung S, et al. 2018. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J. Hepatol.* 68(4):672–81
38. Gupta SK, Post FA, Arribas JR, Eron JJ Jr., Wohl DA, et al. 2019. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. *AIDS* 33(9):1455–65
39. Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, et al. 2019. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *N. Engl. J. Med.* 381(9):803–15
40. Sax PE, Erlandson KM, Lake JE, McComsey GA, Orkin C, et al. 2020. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. *Clin. Infect. Dis.* 71(6):1379–89
41. Calmy A, Tovar Sanchez T, Kouanfack C, Mpoudi-Etame M, Leroy S, et al. 2020. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. *Lancet HIV* 7(10):e677–87
42. Rebeiro PF, Jenkins CA, Bian A, Lake JE, Bourgi K, et al. 2021. Risk of incident diabetes mellitus, weight gain, and their relationships with integrase inhibitor-based initial antiretroviral therapy among persons with human immunodeficiency virus in the United States and Canada. *Clin. Infect. Dis.* 73(7):e2234–42
43. Lu CH, Bednarczyk EM, Catanzaro LM, Shon A, Xu JC, Ma Q. 2021. Pharmacokinetic drug interactions of integrase strand transfer inhibitors. *Curr. Res. Pharmacol. Drug Discov.* 2:100044
44. Chandiwana NC, Serenata CM, Owen A, Rannard S, Perez Casas C, et al. 2021. Impact of long-acting therapies on the global HIV epidemic. *AIDS* 35(Suppl. 2):S137–43
45. Philbin MM, Perez-Brumer A. 2022. Promise, perils and cautious optimism: the next frontier in long-acting modalities for the treatment and prevention of HIV. *Curr. Opin. HIV AIDS* 17(2):72–88
46. Collins S. 2022. CROI 2022: lenacapavir in treatment-experienced participants, and as PrEP in macaques. *HIV Treatment Bulletin*, March 1. **https://i-base.info/htb/42123**
47. Taylor K. 2022. CROI 2022: islatravir studies for HIV treatment and PrEP. *HIV Treatment Bulletin*, March 3. **https://i-base.info/htb/42503**
48. Abrams EJ, Mofenson LM, Pozniak A, Lockman S, Colbers A, et al. 2021. Enhanced and timely investigation of ARVs for use in pregnant women. *J. Acquir. Immune Defic. Syndr.* 86(5):607–15
49. Vitoria M, Ford N, Clayden P, Pozniak AL, Hill AM. 2017. When could new antiretrovirals be recommended for national treatment programmes in low-income and middle-income countries: results of a WHO think tank. *Curr. Opin. HIV AIDS* 12(4):414–22
50. Pepperrell T, Hill A, Moorhouse M, Clayden P, McCann K, et al. 2020. Phase 3 trials of new antiretrovirals are not representative of the global HIV epidemic. *J. Virus Erad.* 6(2):70–73

51. Penazzato M, Irvine C, Vicari M, Essajee SM, Sharma A, et al. 2018. A global research agenda for pediatric HIV. *J. Acquir. Immune Defic. Syndr.* 78(Suppl. 1):S10–15
52. Astawesegn FH, Stulz V, Conroy E, Mannan H. 2022. Trends and effects of antiretroviral therapy coverage during pregnancy on mother-to-child transmission of HIV in Sub-Saharan Africa. Evidence from panel data analysis. *BMC Infect. Dis.* 22(1):134
53. le Roux SM, Abrams EJ, Nguyen KK, Myer L. 2019. HIV incidence during breastfeeding and mother-to-child transmission in Cape Town, South Africa. *AIDS* 33(8):1399–401
54. Adelekan B, Harry-Erin B, Okposo M, Aliyu A, Ndembi N, et al. 2022. Final HIV status outcome for HIV-exposed infants at 18 months of age in nine states and the Federal Capital Territory, Nigeria. *PLOS ONE* 17(2):e0263921
55. Abbas M, Bakhtyar A, Bazzi R. 2022. Neonatal HIV. In *StatPearls*. Treasure Island, FL: StatPearls Publ.
56. Abrams EJ, Mofenson LM, Pozniak A, Lockman S, Colbers A, et al. 2021. Enhanced and timely investigation of ARVs for use in pregnant women. *J. Acquir. Immune Defic. Syndr.* 86(5):607–15
57. Chiappini E, Larotonda F, Lisi C, Giacomet V, Erba P, et al. 2021. Real-world analysis of survival and clinical events in a cohort of Italian perinatally HIV-1 infected children from 2001 to 2018. *Front. Pediatr.* 9:665764
58. Wainberg MA, Mesplede T, Raffi F. 2013. What if HIV were unable to develop resistance against a new therapeutic agent? *BMC Med.* 11:249
59. McCluskey SM, Pepperrell T, Hill A, Venter WDF, Gupta RK, Siedner MJ. 2021. Adherence, resistance, and viral suppression on dolutegravir in sub-Saharan Africa: implications for the TLD era. *AIDS* 35(Suppl. 2):S127–35
60. Inzaule SC, Hamers RL, Bertagnolio S. 2020. Is increasing pretreatment HIV drug resistance a real menace or minor detail? *Lancet HIV* 7(5):e316–17
61. Ávila-Ríos S, Parkin N, Swanstrom R, Paredes R, Shafer R, et al. 2020. Next-generation sequencing for HIV drug resistance testing: laboratory, clinical, and implementation considerations. *Viruses* 12(6):617
62. Howgego GD. 2021. How does HIV persist under antiretroviral therapy: a review of the evidence. *AIDS Rev.* 23(2):65–73
63. Clutter DS, Jordan MR, Bertagnolio S, Shafer RW. 2016. HIV-1 drug resistance and resistance testing. *Infect. Genet. Evol.* 46:292–307
64. Manyana S, Gounder L, Pillay M, Manasa J, Naidoo K, Chimukangara B. 2021. HIV-1 drug resistance genotyping in resource limited settings: current and future perspectives in sequencing technologies. *Viruses* 13(6):1125
65. De Luca A, Hamers RL, Schapiro JM. 2013. Antiretroviral treatment sequencing strategies to overcome HIV type 1 drug resistance in adolescents and adults in low-middle-income countries. *J. Infect. Dis.* 207(Suppl. 2):S63–69
66. Hill AM, Venter F. 2018. The unexpected success of NRTIs in second-line treatment. *Lancet Infect. Dis.* 18:3–5
67. Hakim JG, Thompson J, Kityo C, Hoppe A, Kambugu A, et al. 2018. Lopinavir plus nucleoside reverse-transcriptase inhibitors, lopinavir plus raltegravir, or lopinavir monotherapy for second-line treatment of HIV (EARNEST): 144-week follow-up results from a randomised controlled trial. *Lancet Infect. Dis.* 18(1):47–57
68. Paton NI, Kityo C, Thompson J, Nankya I, Bagenda L, et al. 2017. Nucleoside reverse-transcriptase inhibitor cross-resistance and outcomes from second-line antiretroviral therapy in the public health approach: an observational analysis within the randomised, open-label, EARNEST trial. *Lancet HIV* 4(8):e341–48
69. Wainberg MA. 2004. The impact of the M184V substitution on drug resistance and viral fitness. *Expert Rev. Anti-Infect. Ther.* 2(1):147–51
70. Raffi F, Pozniak AL, Wainberg MA. 2014. Has the time come to abandon efavirenz for first-line antiretroviral therapy? *J. Antimicrob. Chemother.* 69(7):1742–47
71. Inzaule SC, Hamers RL, Doherty M, Shafer RW, Bertagnolio S, Rinke de Wit TF. 2019. Curbing the rise of HIV drug resistance in low-income and middle-income countries: the role of dolutegravir-containing regimens. *Lancet Infect. Dis.* 19(7):e246–52

72. Phillips AN, Bansi-Matharu L, Cambiano V, Ehrenkranz P, Serenata C, et al. 2021. The potential role of long-acting injectable cabotegravir-rilpivirine in the treatment of HIV in sub-Saharan Africa: a modelling analysis. *Lancet Glob. Health* 9(5):e620–27
73. Landovitz RJ, Li S, Eron JJ Jr., Grinsztejn B, Dawood H, et al. 2020. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. *Lancet HIV* 7(7):e472–81
74. Markham A. 2020. Cabotegravir plus rilpivirine: first approval. *Drugs* 80(9):915–22
75. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, et al. 2021. Cabotegravir for HIV prevention in cisgender men and transgender women. *N. Engl. J. Med.* 385(7):595–608
76. Engelman KD, Engelman AN. 2021. Long-acting cabotegravir for HIV/AIDS prophylaxis. *Biochemistry* 60(22):1731–40
77. Hauser A, Goldstein F, Reichmuth ML, Kouyos RD, Wandeler G, et al. 2022. Acquired HIV drug resistance mutations on first-line antiretroviral therapy in southern Africa: systematic review and Bayesian evidence synthesis. *J. Clin. Epidemiol.* 148:135–45
78. Phillips AN, Venter F, Havlir D, Pozniak A, Kuritzkes D, et al. 2019. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. *Lancet HIV* 6(2):e116–27
79. Clayden P. 2017. Preliminary results on dolutegravir use in pregnancy are reassuring. *HIV Treatment Bulletin*, Aug. 10. **https://i-base.info/htb/32182**
80. Cahn P. 2017. Candidates for inclusion in a universal antiretroviral regimen: dolutegravir. *Curr. Opin. HIV AIDS* 12(4):318–23
81. Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, et al. 2021. Dolutegravir or darunavir in combination with zidovudine or tenofovir to treat HIV. *N. Engl. J. Med.* 385(4):330–41
82. Keene CM, Griesel R, Zhao Y, Gcwabe Z, Sayed K, et al. 2021. Virologic efficacy of tenofovir, lamivudine and dolutegravir as second-line antiretroviral therapy in adults failing a tenofovir-based first-line regimen. *AIDS* 35(9):1423–32
83. Marukutira T, Wood BR. 2021. Growing data for recycling tenofovir and lamivudine with dolutegravir as empiric second-line antiretroviral therapy in resource-limited settings. *AIDS* 35(9):1505–7
84. Kantor R. 2021. Next generation sequencing for HIV-1 drug resistance testing-a special issue walkthrough. *Viruses* 13(2):340
85. Moyano A, Ndung'u T, Mann JK. 2022. Determinants of natural HIV-1 control. *AIDS Rev.* 24(2):51–58
86. Mellors JW, Rinaldo CR Jr., Gupta P, White RM, Todd JA, Kingsley LA. 1996. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 272(5265):1167–70
87. Hermans LE, Moorhouse M, Carmona S, Grobbee DE, Hofstra LM, et al. 2018. Effect of HIV-1 low-level viraemia during antiretroviral therapy on treatment outcomes in WHO-guided South African treatment programmes: a multicentre cohort study. *Lancet Infect. Dis.* 18(2):188–97
88. Grimsrud A, Bygrave H, Doherty M, Ehrenkranz P, Ellman T, et al. 2016. Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. *J. Int. AIDS Soc.* 19(1):21484
89. Brennan-Ing M, Ramirez-Valles J, Tax A. 2021. Aging with HIV: health policy and advocacy priorities. *Health Educ. Behav.* 48(1):5–8
90. Shiau S, Bender AA, O'Halloran JA, Sundermann E, Aggarwal J, et al. 2020. The current state of HIV and aging: findings presented at the 10th International Workshop on HIV and Aging. *AIDS Res. Hum. Retroviruses* 36(12):973–81
91. Pahwa S, Deeks S, Zou S, Tomitch N, Miller-Novak L, et al. 2021. NIH workshop on HIV-associated comorbidities, coinfections, and complications: summary and recommendation for future research. *J. Acquir. Immune Defic. Syndr.* 86(1):11–18
92. Peprah E, Armstrong-Hough M, Cook SH, Mukasa B, Taylor JY, et al. 2021. An emerging syndemic of smoking and cardiopulmonary diseases in people living with HIV in Africa. *Int. J. Environ. Res. Public Health* 18(6):3111
93. van Riel SE, Klipstein-Grobusch K, Barth RE, Grobbee DE, Feldman C, et al. 2021. Predictors of impaired pulmonary function in people living with HIV in an urban African setting. *South Afr. J. HIV Med.* 22(1):1252
94. Bourgi K, Wanjalla C, Koethe JR. 2018. Inflammation and metabolic complications in HIV. *Curr. HIV/AIDS Rep.* 15(5):371–81

95. Godfrey C, Bremer A, Alba D, Apovian C, Koethe JR, et al. 2019. Obesity and fat metabolism in human immunodeficiency virus-infected individuals: immunopathogenic mechanisms and clinical implications. *J. Infect. Dis.* 220(3):420–31
96. Peterson TE, Baker JV. 2019. Assessing inflammation and its role in comorbidities among persons living with HIV. *Curr. Opin. Infect. Dis.* 32(1):8–15
97. Sereti I, Krebs SJ, Phanuphak N, Fletcher JL, Slike B, et al. 2017. Persistent, albeit reduced, chronic inflammation in persons starting antiretroviral therapy in acute HIV infection. *Clin. Infect. Dis.* 64(2):124–31
98. Baker JV, Sharma S, Achhra AC, Bernardino JI, Bogner JR, et al. 2017. Changes in cardiovascular disease risk factors with immediate versus deferred antiretroviral therapy initiation among HIV-positive participants in the START (Strategic Timing of Antiretroviral Treatment) trial. *J. Am. Heart Assoc.* 6(5):e004987
99. Kettelhut A, Bowman E, Funderburg NT. 2020. Immunomodulatory and anti-inflammatory strategies to reduce comorbidity risk in people with HIV. *Curr. HIV/AIDS Rep.* 17(4):394–404
100. Shah S, Hindley L, Hill A. 2021. Are new antiretroviral treatments increasing the risk of weight gain? *Drugs* 81(3):299–315
101. Erlandson KM, Carter CC, Melbourne K, Brown TT, Cohen C, et al. 2021. Weight change following antiretroviral therapy switch in people with viral suppression: pooled data from randomized clinical trials. *Clin. Infect. Dis.* 73(8):1440–51
102. Surial B, Mugglin C, Calmy A, Cavassini M, Gunthard HF, et al. 2021. Weight and metabolic changes after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in people living with HIV: a cohort study. *Ann. Intern. Med.* 174(6):758–67
103. Lake JE, Trevillyan J. 2021. Impact of integrase inhibitors and tenofovir alafenamide on weight gain in people with HIV. *Curr. Opin. HIV AIDS* 16(3):148–51
104. Venter WDF, Sokhela S, Simmons B, Moorhouse M, Fairlie L, et al. 2020. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV* 7(10):e666–76
105. Ruderman SA, Crane HM, Nance RM, Whitney BM, Harding BN, et al. 2021. Brief report: weight gain following ART initiation in ART-naive people living with HIV in the current treatment era. *J. Acquir. Immune Defic. Syndr.* 86(3):339–43
106. Heymsfield SB, Wadden TA. 2017. Mechanisms, pathophysiology, and management of obesity. *N. Engl. J. Med.* 376(15):1492
107. Wharton S, Lau DCW, Vallis M, Sharma AM, Biertho L, et al. 2020. Obesity in adults: a clinical practice guideline. *Can. Med. Assoc. J.* 192(31):E875–91
108. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, et al. 2021. Once-weekly semaglutide in adults with overweight or obesity. *N. Engl. J. Med.* 384(11):989–1002
109. Vos AG, Venter WDF. 2021. Cardiovascular toxicity of contemporary antiretroviral therapy. *Curr. Opin. HIV AIDS* 16(6):286–91
110. Baxevanidi EE, Sumbul A, Qavi A, Hill A, Venter F, et al. 2021. *Predicted long-term adverse birth and child health outcomes in the ADVANCE trial*. Paper presented at the Conference on Retroviruses and Opportunistic Infections, virtual, March 6–10
111. Asif S, Baxevanidi E, Hill A, Venter WDF, Fairlie L, et al. 2021. The predicted risk of adverse pregnancy outcomes as a result of treatment-associated obesity in a hypothetical population receiving tenofovir alafenamide/emtricitabine/dolutegravir, tenofovir disoproxil fumarate/emtricitabine/dolutegravir or tenofovir disoproxil fumarate/emtricitabine/efavirenz. *AIDS* 35(Suppl. 2):S117–25
112. McCann K, Shah S, Hindley L, Hill A, Qavi A, et al. 2021. Implications of weight gain with newer anti-retrovirals: 10-year predictions of cardiovascular disease and diabetes. *AIDS* 35(10):1657–65
113. Spinelli MA, Haberer JE, Chai PR, Castillo-Mancilla J, Anderson PL, Gandhi M. 2020. Approaches to objectively measure antiretroviral medication adherence and drive adherence interventions. *Curr. HIV/AIDS Rep.* 17(4):301–14

114. Drain PK, Bardon AR, Simoni JM, Cressey TR, Anderson P, et al. 2020. Point-of-care and near real-time testing for antiretroviral adherence monitoring to HIV treatment and prevention. *Curr. HIV/AIDS Rep.* 17(5):487–98
115. Berg RC, Page S, Ogard-Repal A. 2021. The effectiveness of peer-support for people living with HIV: a systematic review and meta-analysis. *PLOS ONE* 16(6):e0252623
116. Beletsky L, Thumath M, Haley DF, Gonsalves G, Jordan A. 2021. HIV's trajectory: biomedical triumph, structural failure. *Am. J. Public Health* 111(7):1258–60
117. Mateo-Urdiales A, Johnson S, Smith R, Nachega JB, Eshun-Wilson I. 2019. Rapid initiation of antiretroviral therapy for people living with HIV. *Cochrane Database Syst. Rev.* 6:CD012962
118. Rosen S, Maskew M, Brennan AT, Fox MP, Vezi L, et al. 2018. Improved simplified clinical algorithm for identifying patients eligible for immediate initiation of antiretroviral therapy for HIV (SLATE II): protocol for a randomized evaluation. *Trials* 19(1):548
119. Bygrave H, Golob L, Wilkinson L, Roberts T, Grimsrud A. 2020. Let's talk chronic disease: Can differentiated service delivery address the syndemics of HIV, hypertension and diabetes? *Curr. Opin. HIV AIDS* 15(4):256–60
120. Ford N, Geng E, Ellman T, Orrell C, Ehrenkranz P, et al. 2020. Emerging priorities for HIV service delivery. *PLOS Med.* 17(2):e1003028
121. Jandoo T. 2020. WHO guidance for digital health: what it means for researchers. *Digit. Health* 6:2055207619898984
122. WHO (World Health Organ.). 2019. *Recommendations on digital interventions for health system strengthening*. WHO Guidel., Geneva, Switz.
123. Moodley S, Gray A, Schellack N, Venter F, Suleman F, et al. 2021. Pharmacist-initiated antiretroviral therapy (PIMART). *S. Afr. Med. J.* 111(12):1162–63
124. Kennedy CE, Yeh PT, Atkins K, Ferguson L, Baggaley R, Narasimhan M. 2022. PrEP distribution in pharmacies: a systematic review. *BMJ Open* 12(2):e054121
125. Meintjes G, Brust JCM, Nuttall J, Maartens G. 2019. Management of active tuberculosis in adults with HIV. *Lancet HIV* 6(7):e463–74
126. Shroufi A, Chiller T, Jordan A, Denning DW, Harrison TS, et al. 2021. Ending deaths from HIV-related cryptococcal meningitis by 2030. *Lancet Infect. Dis.* 21(1):16–18
127. Lerner AM, Eisinger RW, Fauci AS. 2020. Comorbidities in persons with HIV: the lingering challenge. *JAMA* 323(1):19–20
128. Lee MJ, Fidler S, Frater J. 2022. Immunotherapeutic approaches to HIV cure and remission. *Curr. Opin. Infect. Dis.* 35(1):31–41
129. Dybul M, Attoye T, Baptiste S, Cherutich P, Dabis F, et al. 2021. The case for an HIV cure and how to get there. *Lancet HIV* 8(1):e51–58
130. Lewin SR, Attoye T, Bansbach C, Doehle B, Dube K, et al. 2021. Multi-stakeholder consensus on a target product profile for an HIV cure. *Lancet HIV* 8(1):e42–50
131. Devanathan AS, Cottrell ML. 2021. Pharmacology of HIV cure: site of action. *Clin. Pharmacol. Ther.* 109(4):841–55
132. Fletcher CV, Dyavar SR, Acharya A, Byrareddy SN. 2021. The contributions of clinical pharmacology to HIV cure research. *Clin. Pharmacol. Ther.* 110(2):334–45
133. Migliori GB, Tiberi S, Zumla A, Petersen E, Chakaya JM, et al. 2020. MDR/XDR-TB management of patients and contacts: challenges facing the new decade. The 2020 clinical update by the Global Tuberculosis Network. *Int. J. Infect. Dis.* 92S:S15–25
134. Cambiano V, Lampe F, Miners A, McCormack S, Gill N, et al. 2022. *Contributions to the decline in HIV incidence among GBM in the UK: a modelling study*. Paper presented at the Conference on Retroviruses and Opportunistic Infections, virtual, Febr. 11–16
135. Wymant C, Bezemer D, Blanquart F, Ferretti L, Gall A, et al. 2022. A highly virulent variant of HIV-1 circulating in the Netherlands. *Science* 375(6580):540–45
136. Cohen MS, Gamble T, McCauley M. 2020. Prevention of HIV transmission and the HPTN 052 study. *Annu. Rev. Med.* 71:347–60

137. Laher F, Richardson SI, Smith P, Sullivan PS, Abrahams AG, et al. 2021. HIV prevention in a time of COVID-19: a report from the HIVR4P // virtual conference 2021. *AIDS Res. Hum. Retroviruses* 38(5)350–58
138. Bavinton BR, Grulich AE. 2021. HIV pre-exposure prophylaxis: scaling up for impact now and in the future. *Lancet Public Health* 6(7):e528–33
139. Bor J, Onoya D, Richman B, Mayer KH. 2021. A failure to disseminate transformative science—HIV treatment as prevention, 10 years on. *N. Engl. J. Med.* 385(25):2305–7
140. Dieffenbach CW, Fauci AS. 2020. The search for an HIV vaccine, the journey continues. *J. Int. AIDS Soc.* 23(5):e25506
141. Enoch J, Piot P. 2017. Human rights in the fourth decade of the HIV/AIDS response: an inspiring legacy and urgent imperative. *Health Hum. Rights* 19(2):117–22
142. Honermann B, O'Hagan R. 2017. Use of expenditure analysis to enhance returns on investments in HIV services. *Curr. Opin. HIV AIDS* 12(5):494–500
143. Maartens G, Celum C, Lewin SR. 2014. HIV infection: epidemiology, pathogenesis, treatment, and prevention. *Lancet* 384(9939):258–71
144. INSIGHT START Study Group. 2015. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N. Engl. J. Med.* 373(9):795–807

RELATED RESOURCES

WHO (World Health Organ.) HIV/AIDS: **https://www.who.int/health-topics/hiv-aids#tab=tab_1**. WHO produces exhaustively reviewed guidelines that assist countries throughout the world to adapt to their local circumstances.

UNAIDS AIDSinfo: **https://aidsinfo.unaids.org/**. UNAIDS provides updates on the global, regional, and country-specific state of the epidemic.

HIV Treatment Bulletin: **https://i-base.info/htb/**. This website, compiled by independent activists, is a remarkable compilation of HIV new diagnostics and medications in development, with reviews of breaking conference data and an annual overview of each candidate medication and the current state of development.

Clinical Care Options: **https://www.clinicaloptions.com/?q&sortBy&sortOrder=asc&page=1**. USA-based Clinical Care Options provides excellent slide decks, podcasts, webinars, and discussion blogs, among others.

Academic Medical Education: **https://academicmedicaleducation.com/about-ve**. A Europe-based and more global speaker bureau.

Southern African HIV Clinicians Society: **https://sahivsoc.org/Subheader/Index/sahcs-guidelines**. A large repository of resources focused on southern Africa.

AVAC: **https://www.avac.org/**. An up-to-date collection of reliable resources on the state of HIV prevention.