Antiretroviral products for HIV prevention
Looking toward 2031

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**Antiretroviral Products for HIV Prevention: Looking toward 2031**

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**Introduction**

The development of safe and effective antiretroviral agents (ARVs) has been among the greatest advances in the response to the HIV/AIDS epidemic. ARVs were introduced in the mid-1980s as treatment for HIV infection and were initially used as single agents and later in two-drug combinations.¹ However, treatment benefits were modest because HIV quickly developed resistance to the single or double ARVs used.² In 1996, the use of triple-drug antiretroviral therapy (ART) with nucleotide reverse transcriptase inhibitors and protease inhibitors, a new class of ARV, was shown to be highly effective in treating HIV infection and produced dramatic clinical improvements.³

Since ART reduces the level of HIV in the blood and male and female genital secretions,⁴ it follows that ART could also prevent HIV transmission by decreasing infectiousness. The concept of using ART to prevent sexual and blood-borne transmission is strengthened by observations about mother-to-child HIV transmission. Zidovudine administered to HIV-infected women during pregnancy/labor and to their newborn children was found to reduce mother-to-child HIV transmission by two-thirds, from 26% to 8%.⁵ Subsequently, more potent combination ART regimens have reduced the mother-to-child transmission rate to less than 2%.⁶ The degree of effectiveness of these regimens is highly correlated with their ability to reduce the mother’s HIV viral level in the blood and in cervical-vaginal secretions.⁷⁻⁹

In 1997, observational data were used to support ART as post-exposure prophylaxis. ART regimens taken by health-care workers who had sustained occupational exposures to HIV (e.g., a needle stick with HIV-infected blood) had greatly reduced risk of HIV acquisition.¹⁰
Additional evidence that ART could be used to prevent HIV transmission came from laboratory studies of monkeys (rhesus macaques) exposed to an HIV-like virus (simian immunodeficiency virus [SIV] or SHIV, an SIV-HIV chimeric virus). Monkeys administered ART either before or after viral challenge were protected from infection; the more potent the ART regimen and the higher the concentration of drugs, the greater the protection.\textsuperscript{11-13}

**Current Approaches to ART for Prevention**

ART can be used for HIV prevention in three main ways (reviewed by Cohen et al., 2007\textsuperscript{14} and Gay & Cohen, 2008\textsuperscript{15}): 

1) **treating** HIV-infected persons to lower their viral level and hence decrease their infectiousness

2) providing **post-exposure** prophylaxis to HIV-uninfected persons after a risk-related HIV exposure (sexual or needle sharing), or

3) providing **pre-exposure** prophylaxis to HIV-uninfected persons to prevent the establishment of HIV infection when they are exposed to HIV.

**ART to decrease infectiousness**

The transmission of HIV via sexual, blood-borne or perinatal routes is highly associated with the HIV viral level measured in the blood. In Uganda, increased plasma HIV levels were strongly associated with higher rates of sexual HIV transmission to partners.\textsuperscript{16,17} Additional studies of HIV serodiscordant couples in Zambia and Thailand found a similar association.\textsuperscript{18,19} Therefore, the reduction of HIV viral levels with ART should be associated with decreased HIV transmission during exposure to an HIV-uninfected person.

Several retrospective and prospective observational studies have suggested that treating the HIV-infected partner in a serodiscordant couple with ART was associated with substantial reduced transmission to the HIV-uninfected partner.\textsuperscript{20-23} An ongoing, large, multi-country, randomized, controlled trial is evaluating the impact of early initiation of ART (above the standard CD4 count for ART initiation) on HIV transmission within HIV discordant couples (HPTN-052).
In early 2008, the Swiss Federal Commission on HIV/AIDS issued a statement suggesting that persons receiving ART that produced non-detectable plasma HIV levels and without other sexually transmitted infections were so “non-infectious” that condom use with sexual partners was not necessary.\textsuperscript{24} The opinion was quite controversial and was not endorsed by UNAIDS, the World Health Organization or the US Centers for Disease Control and Prevention.\textsuperscript{25,26} Much of the data informing the Swiss statement was from HIV serodiscordant heterosexual couples. However, if the transmission threshold is lower for penile-anal sex than for penile-vaginal sex, extrapolating from heterosexual couples to men-who-have-sex-with-men (MSM) would not be appropriate. A model based analysis suggested that the risk of HIV transmission in heterosexual partnerships in the presence of effective ART was low, but not zero, and that risk in male homosexual partnerships was high over repeated exposures.\textsuperscript{26} This analysis provides reason for caution before accepting the recommendation to forego condom use in this situation.

In addition, the proposed optimal timing of the initiation of ART has evolved since highly-active ART (HAART) was introduced in 1996. Initially, the approach was to “hit early and hit hard” to maximally suppress HIV replication and to preserve immune function. However, the drugs used for ART were observed to have substantial adverse effects and recommendations evolved to start ART later in the course of disease progression (e.g., when the CD4 cell count fell to 350/\(\mu\)L). The goal was to strike a balance between limiting immune system damage caused by HIV and minimizing adverse and long term effects of treatment. Furthermore, in the resource-limited regions of the world with most of the global burden of HIV disease, ART was generally started later (e.g., when the CD4 cell count fell to 250/\(\mu\)L or 200/\(\mu\)L) for cost-savings and logistical reasons. However, a recent report of observational data from the United States and Canada suggests that starting ART when the CD4 cell count is between 350/\(\mu\)L and 500/\(\mu\)L offers a 70% advantage in all cause mortality survival compared to starting ART when the count falls below 350/\(\mu\)L.\textsuperscript{27} These and other results may “swing the pendulum” toward much earlier therapy.

Substantial, irreversible damage to the immune system occurs during the first days of infection.\textsuperscript{28} In addition, HIV may be readily transmitted from subjects with acute and early infection,\textsuperscript{17} perhaps because of very high “peak viral loads.”\textsuperscript{29} Future improvements
in HIV screening programs and new diagnostic tools may increase detection of persons who are acutely HIV infected (i.e., before seroconversion on current HIV screening tests). Prompt diagnosis of newly HIV-infected persons and early initiation of ART (especially with newer drugs that reduce viral levels promptly and/or concentrate in genital secretions) could make a contribution to the interruption of HIV transmission networks and an overall reduction in HIV incidence. Furthermore, persons who know they are HIV-infected and receive prevention counseling have been shown to sharply reduce their risky behaviors. In the United States, the estimated 25% of persons who do not know they are HIV infected account for more than half of the new sexually transmitted HIV infections each year. Therefore, the development of improved diagnostic tests, better HIV screening programs and easier-to-tolerate, effective ART would work synergistically to dramatically reduce HIV transmission.

**Post-exposure prophylaxis with ART**

The use of post-exposure prophylaxis for occupational exposures is now considered standard of care for health care workers in many countries. While considerable interest exists in the use of post-exposure prophylaxis for non-occupational exposures, a randomized, controlled trial of ART prophylaxis after non-occupational HIV exposure is not feasible. The sample size required for such a study is prohibitive, both in recruitment and cost, due to the relative inefficiency of sexual transmission per exposure.

Nevertheless, the use of ART prophylaxis after non-occupational exposure is expanding worldwide. The first US guidelines for non-occupational post-exposure prophylaxis were issued in 2005; they recommend a three-drug regimen for 28 days following high-risk sexual exposure to a known or suspected HIV-infected partner. Non-occupational post-exposure ART is acceptable and adherence is quite high, with 64% to 100% completion rates for 28-day ART regimens.

While the efficacy of post-exposure ART prophylaxis has not been defined, failures have been described. Seven HIV seroconversions were reported among 702 persons who received two or three ARVs for 28 days with 12 weeks of follow up. Four of the seven seroconversions were considered post-exposure failures, since 100% adherence
to the ART regimen was reported; the failures were associated with anal intercourse exposure and delayed initiation of ART. Three of the persons who seroconverted started ART more than 55.5 hours after exposure, which is within the 72-hour window for which post-exposure prophylaxis is recommended. Our current understanding of HIV transmission suggests that post-exposure prophylaxis should be started as soon after the exposure as possible with a potent ART regimen. It is important to provide education and support to front-line health care professionals managing these decisions.

**Pre-exposure prophylaxis with ART**

The concept of ART pre-exposure prophylaxis needs a new lexicon of terminology. Delivery can be by oral ART pills, topical (vaginal or anal) ARV formulations such as gels, films, suppositories or rings, or injectable/implantable ARV. Moreover, the products can be used on a daily or an intermittent (sexual event or regular periodic) basis. We avoid use of non-specific terms like “PrEP” or “microbicides” since these are merely synonyms for oral use and topical use, respectively, of ART for prevention. To date, non-specific topical products (vaginal defense boosters, surfactants, and entry inhibitors) have not proven effective.

The use of ART by HIV-uninfected persons before exposure to HIV was based on laboratory studies of rhesus macaque monkeys challenged with HIV-like viruses. A repeat low-dose virus challenge monkey model has allowed for the evaluation of various timing and dosing regimens to guide the design of human clinical trials. In general, more potent ART regimens are associated with higher levels of protection. A combination of tenofovir and emtricitabine provided more protection that either drug alone and a higher dose of the drug combination administered by subcutaneous injection was more protective than a lower dose administered orally.

Seven human, randomized, placebo-controlled, clinical trials of the safety and efficacy of oral ART pre-exposure are either ongoing (five trials) or planned to start (two trials) in 2009. These trials are slated to enroll nearly 20,000 HIV-uninfected persons at risk for HIV infection. They include men-who-have-sex-with-men (MSM) in the United States (n=400; tenofovir), injection drug users in Bangkok, Thailand (n=2400; tenofovir), heterosexual men and women in Botswana (n=1800 or 2000; tenofovir-emtricitabine
[Truvada®]), MSM in several countries in the Americas, Africa and Asia (n=3000; tenofovir-emtricitabine), discordant heterosexual couples in Kenya and Uganda (n=3,900 couples; tenofovir, tenofovir-emtricitabine), and women in Africa (n=8,100 in two studies). The FEM-PrEP trial being planned among women in Africa will evaluate oral tenofovir-emtricitabine compared to placebo, while the VOICE study (or MTN-003) will evaluate oral tenofovir, oral tenofovir-emtricitabine, and topical tenofovir 1% gel in a 5-arm trial (including an oral and gel placebo arm) among African women.

Topical ART use is also being studied. An ongoing trial in South Africa (CAPRISA-004) is evaluating the safety and efficacy of tenofovir 1% gel for vaginal use compared to a placebo gel to prevent sexually transmitted HIV infection. In contrast to the daily use of oral ART currently being evaluated, in CAPRISA-004, the gel is applied both before and after an episode of vaginal intercourse, but not more than 2 doses in a 24-hour interval.

To date, only one clinical trial of pre-exposure ART (oral tenofovir) among 936 women in Ghana, Nigeria and Cameroon has been completed.51 This study provided important data on the safety of tenofovir in this setting and indicated that women did not report increasing their risk behaviors. No significant differences in clinical or laboratory adverse events occurred between women receiving tenofovir or placebo. Unfortunately, this study was not carried to completion in Cameroon and Nigeria and was consequently unable to assess the efficacy of this regimen in preventing HIV infection. Eight HIV infections occurred among study participants, six among placebo recipients and two among women on tenofovir (p=0.24); this difference is not statistically significant. Among the only intercurrent HIV infection studied, no viral resistance to tenofovir was observed.52

The trials of oral pre-exposure ART have been plagued by controversy.53 In Cambodia, a planned study of oral tenofovir was not started due to community concerns about the study design and participant benefits, which led to political opposition.54 In Cameroon, similar community and political opposition contributed to the pre-mature closure of this site in the 3-country West Africa oral tenofovir study.51 In other current and potential trial sites, ongoing concerns about the development of tenofovir resistance have been raised, slowing or even aborting planned studies.

**Other Issues in ART for Prevention**
**Timing of drug delivery**

Most ongoing trials of ART for pre-exposure prophylaxis are evaluating daily, oral administration of the study drug, either tenofovir or tenofovir-emtricitabine (formulated in a single pill). These drugs have a favorable safety profile and a therapeutic drug level which can be maintained with once-daily dosing. The current trials will establish whether daily dosing with the study drug is effective in reducing the risk of HIV acquisition, and also if the drugs are safe to use in this manner. However, daily dosing is impractical for many people at risk for HIV infection, especially persons with an irregular or unpredictable pattern of sexual activity. Thus, investigating intermittent or periodic ART regimens suitable to the wide variety of HIV risk exposure patterns experienced by heterogeneous populations will be crucial. To help guide human clinical trials a series of monkey experiments are evaluating various dosing regimens at different times before and after challenge with the HIV-like virus.\textsuperscript{13} In addition, a novel mouse model may contribute to these considerations.\textsuperscript{55}

In preparation for possible intermittent ART trials among HIV-uninfected persons, information on the frequency of sexual exposure and whether or not sexual exposures are predictable is needed. In Bangkok, Thailand, sexual activity among MSM was highly predictable. Most men reported sex 2 days or fewer per week, suggesting an intermittent regimen of ART for pre-exposure prophylaxis would be desirable and feasible in this population.\textsuperscript{56} However, sexual exposure is neither predictable nor within the control of many people at risk for HIV infection; ART for prevention, either daily or intermittent, will need to be customized for specific settings.

Only one ongoing human clinical trial (CAPRISA 004 described above) is evaluating vaginal use of coitally-dosed tenofovir 1% gel compared to placebo gel. This study should yield efficacy results in 2010. To help guide future topical gel trials, a new monkey model has been developed to evaluate repeat vaginal challenge with an HIV-like virus (SHIV); study gel was administered vaginally 30 minutes before vaginal SHIV challenge. Data from a recent study showed complete protection of six monkey receiving SHIV challenge 20 times compared to control monkeys. Seven of eight controls became infected after a median of 3.5 challenges (P<0.005).\textsuperscript{57} The relative merits of oral or topical (vaginal or rectal) ART will be informed by the results on ongoing clinical trials.
Longer-lasting ART for HIV-uninfected persons could be also administered in an injectable or implantable formulation, as well as by vaginal devices. The field should be informed by the extensive and long history of contraceptive technology that includes oral, vaginal, injectable and implantable forms of hormonal contraception.

**Mode of HIV Transmission**

Mode of HIV transmission will be an important consideration for the use of ART for prevention. The protective threshold for ART may be different between parenteral and sexual challenge, and for sexual routes, whether the mode is receptive vaginal, receptive anal, or insertive vaginal or anal. The per-sex-act probability of HIV is substantially higher for receptive anal sex than for other sexual modes. Consequently, treating an HIV-infected person with ART, which results in reduced HIV levels and infectiousness, may be less effective, in absolute terms, for preventing penile-anal transmission than penile-vaginal transmission.

Obviously, mode of transmission is central to considerations for use of topical ART for prevention. Topical agents, including ARVs, have primarily been evaluated for protection of penile-vaginal transmission. The development of effective topical agents for anal use will require a separate research agenda accounting for the important differences in anatomy, histology and physiology involved. Importantly, recent data suggest that topical ART administered anally achieves high concentrations in local tissue and is rapidly absorbed resulting in blood levels similar to orally administered ART.

**How would ART be used for HIV Prevention for HIV-uninfected Persons**

If ART for prevention for HIV-uninfected persons is found to be safe and effective, a major effort will be required to develop strategies for the roll-out of programs. Just as with adolescent and adult male circumcision, ART prophylaxis will need to be integrated into a comprehensive HIV prevention strategy.

**What Drugs?**

The selection of drug resistant HIV strains has been a substantial concern for use of ART prevention strategies. With the increasing number of available ART for treatment, some agents or a class of agents might be “saved” for prevention. If such a strategy was employed, ART resistance to the ART prevention agent would not compromise ART
treatment options for the newly infected person who became HIV infected despite ART prophylaxis as long as no cross resistance developed between the prevention agent (or class of agent) and the drugs used for treatment.

Current ART for prevention regimens being tested among HIV-uninfected persons include tenofovir and the single-pill combination of tenofovir-emtricitabine (Truvada®). Additional drugs likely will be evaluated for prevention, perhaps leading to triple-drug prophylaxis. A multi-drug regimen would likely be more effective and would decrease the probability of the emergence of drug resistant HIV strains. However, such a regimen would also be more costly and could have more adverse effects.

What Populations?
The process of determining how to use ART for HIV-uninfected persons, in which populations, when, and for how long will likely be complicated and controversial. Throughout the world, HIV-negative persons in partnerships with HIV-infected persons will likely be a high priority. In concentrated epidemics, MSM and injection drug users continue to account for a substantial proportion of new HIV infections; thus, they likely will be considered for ART prevention. Prophylactic ART could be prescribed by individual providers apart from a broader public health program. The decision of who pays for PrEP would be determined by local considerations and could include a national health service, other governmental programs, private insurance, or fee-for-service.

In resource-limited nations with generalized epidemics, targeting population subgroups for ART prophylaxis will require thoughtful consideration. While some individuals would be able to pay for ART, for the vast majority this intervention would only be available via a subsidized program. At the national level, populations at high risk for HIV infection can be identified from available epidemiologic and surveillance data. In many African countries, young women, beginning in their teenage years, are at particularly high risk for HIV infection. The provision of prophylactic ART to adolescents will likely generate considerable discussion, particularly in the way in which the program is offered or provided along with support for delaying sexual debut, partner reduction, condom provision and contraception. Current clinical trials of ART for prevention discourage women from becoming pregnant while in the study and often require use of an effective method of contraception. Programmatic use of ART for women of child-bearing
age will need to address the woman’s intentions to become pregnant and her varying alternatives for prevention.

In nations with concentrated epidemics, analysis of available data can be used to identify most at-risk populations. For some countries injection drug users would be a high priority, for others MSM or sex workers. Focusing on intervals at highest risk, and selectively using prophylactic ART for highest exposure events provides an optimal public health impact.

**Behavioral Enhancement**

Like all interventions for HIV-uninfected persons, ART will be only partially effective, which will necessitate ongoing HIV risk reduction efforts. A major concern is behavioral enhancement, also known as risk compensation and risk behavior disinhibition. This is defined as an increase in risk behavior associated with a preventive intervention. Behavioral enhancement is mediated by the perceived efficacy of the biomedical intervention and decreased perception of risk. Efforts to prevent behavioral enhancement will need to accompany the introduction of ART prophylaxis, as is currently being done with the scale up of male circumcision programs in Africa.

Behavioral enhancement might affect prevention gains offered by prophylactic ART if protection afforded is less than perfect. A modeling exercise evaluated the introduction of ART for prevention in an African setting and assessed the impact of behavioral enhancement along with other factors. In this model, if the effectiveness of prophylactic ART is less than 50% and if risky behavior doubles, an increase in HIV infections in the population would occur. This finding underscores the importance of strengthening HIV risk reduction programs when any new biomedical interventions are introduced. Programs to support HIV prevention education, condom provision and use, partner reduction, and STI management should be supported.

**Dosing Strategies**

Daily ART prophylaxis would provide the most consistent level of protection. However, daily use for a prolonged period of time will not be practical or acceptable for many persons at risk for HIV. An effective regimen that could be used intermittently - either just before or just after (or both) a risky exposure - would greatly simplify use. Even if a regimen included a few days of ART after an exposure, for many people intermittent
use would result in fewer does of drug than a daily regimen. An intermediate strategy could include a periodic (weekly or semi-weekly) dose to maintain a minimal drug level that would be augmented before/after the specific risk exposure.

Currently, health care workers who experience an occupational exposure to HIV are evaluated to characterize the nature of the exposure, have a blood collected for testing and, if deemed appropriate are started on a post-exposure ART regimen. For people in the community, non-occupational post-exposure prophylaxis requires a visit to a health care facility for evaluation and initiation of ART. For an intermittent ART regimen (that could include pre- and post-exposure dosing), advanced provision of the ART (“emergency HIV prevention”) would be possible for use at the time of a planned or unplanned exposure.

**ARV Resistance**

The selection of ARV-resistant HIV strains by persons on prophylaxis, and their subsequent transmission, has been a major concern for both clinical trials and eventual programmatic use of ART for prevention. Ongoing and planned clinical trials of ART PrEP will carefully assess ARV resistance in the HIV strains that establish infection. However, it is likely that the use of ART for the treatment of HIV-infected persons will continue to be the major source of ARV-resistant HIV strains.

**Medical Personnel and Prevention**

In many settings in the world, HIV prevention services are provided in non-medical facilities without physicians. Services are often provided by community-based organizations (CBOs) who refer clients to health facilities when they are found to be HIV-infected or when they require medical evaluation of treatment. The introduction of ART for prevention for HIV-uninfected persons would require arrangements for physicians or other health care professionals to prescribe ART. Lessons learned from ongoing efforts to shift ART treatment tasks to non-physicians in many resource-limited countries will inform the development of programs for ART for prevention for HIV-uninfected persons.

**Programmatic Implementation**

When prophylactic ART is shown to be safe and effective in preventing HIV infection, there will be great demand for this new prevention modality. UNAIDS and the US Centers for Disease Control and Prevention have already initiated processes to guide
eventual programmatic implementation of prophylactic ART. Pilot programs among the highest risk populations in various settings to assess impact and inform further programmatic implementation. However, since the drugs to be used for prophylactic ART are already available and being used for treatment, it will be possible for providers in some settings to prescribe ART for prevention before official recommendations are made. Indeed, ART PrEP is already being used on a limited basis by some high-risk individuals without evidence that it is effective.\textsuperscript{66}

When male circumcision was shown to be effective in reducing the risk of acquiring HIV, initial recommendations were made to scale up male circumcision programs in areas of the world with high rates of heterosexual HIV transmission and low rates of male circumcision.\textsuperscript{67} Geography will also play a role in deciding where early ART for prevention programs will be initiated. Persons in specific high-risk population sub-groups in concentrated epidemics and young adults in generalized epidemics will warrant early consideration for programs.

**Mathematical Modeling**

There have been several models developed to predict the impact of ART on per-couple HIV transmission,\textsuperscript{26,68-71} reduction of HIV at the population level,\textsuperscript{72-75} and the effects of prophylactic ART.\textsuperscript{65,76} These models are entirely bounded by assumptions about the degree and durability of benefit of ART, the number of people who can be reached, behavioral changes, ARV resistance, and sexual mixing patterns. None of these models have been tested and, for the most part, the empirical data used to support the modeling is limited. As we try to look forward to 2031, we believe that modeling has limited power to predict the future.

**What will the ART prevention landscape look like in 2031?**

In 2031, it is unlikely that curative HIV treatment will be available. It is also unlikely that an HIV vaccine that prevents infection will be available. It is more likely that a vaccine will be available that does not prevent HIV infection, but does stimulate an immune response that results in a reduced viral level set point. Such a vaccine would result in less severe HIV infection (i.e., with slower progression to disease) and would reduce HIV transmission, including during the acute infection period.
Male circumcision will have been implemented widely in some regions with high rates of heterosexual HIV transmission, especially in Africa, resulting in some decreased transmission. However, coverage will lag in many areas due to a combination of acceptability, cultural and logistical barriers. It is unlikely that male circumcision will be implemented widely in most parts of Asia, including China and India. It is unclear how widely infant circumcision will be implemented in the countries with the highest burden of HIV, but it is likely that a failure to implement infant circumcision programs will be viewed as a missed opportunity when the generation born in 2008-2018 reaches adolescence in the coming decades.

Advances will be made in behavioral and structural interventions; however, their impact will be limited. Other sexually transmitted diseases (STDs) will continue to serve as important co-factors for HIV transmission. STD control will continue to be based on behavioral risk reduction, condom use and antibiotic therapy as it is unlikely that new STD vaccines will be available. While efforts are being made to develop a vaccine for herpes simplex virus type 2 (HSV-2), the current vaccine has limited efficacy only for women who are both HSV-1 and HSV-2-negative.77

Technological advances in HIV diagnostics and ART will allow for substantial advances in HIV prevention. One of the most striking failures in HIV prevention over the past two decades has been the limited proportion of HIV-infected persons who know their status. In many countries with generalized epidemics, a minority of HIV-infected persons knows their status, while in the United States, an estimated 25% remain unaware they are HIV-positive. Current highly-accurate, rapid HIV tests are terribly underutilized even in obvious settings such as STD care clinics. Over the next two decades, prevention efforts will focus heavily on reducing the stigma related to HIV and increasing coverage and access to HIV testing and linkage to prevention and care services.

HIV diagnostic tests will improve substantially. Rapid, inexpensive, point-of-care tests that can determine both acute and established HIV infection status are already in development. Rapid tests will also be available to determine the HIV viral level and the level of immune function, e.g., CD4 cell count. Such improved diagnostic tests will make the new diagnosis of a person with advanced HIV infection (and a low CD4 cell count) a rare event. HIV prevention efforts will increasingly be related to the viral level detected at
the time of diagnosis. Because people with higher viral levels represent a greater risk of HIV transmission (whether they have acute or established infection) they will be prioritized for HIV prevention.

ART will be easier to administer and be associated with fewer adverse effects. Consequently, ART will be started at the time of HIV diagnosis, not rationed by stage of disease progression as measured by CD4 cell count or by HIV blood levels. Long-acting ART formulations, either by injection or implant may be available. Globally, tens of millions of HIV-infected persons will be on ART for the control and prevention of HIV infection. With broad coverage of ART among persons know to be HIV-infected and the resulting decrease in HIV transmission, known HIV-infected persons will account for a smaller proportion of new transmission events. However, persons failing ART due to HIV resistance or non-adherence to their regimen will transmit HIV-resistant infections. Persons living with undiagnosed HIV infection, including those with acute infection, will be the source of a large majority of new HIV infections.

However, achieving broad ART program coverage for HIV-infected persons will remain a challenge in some areas and for some populations, especially in places where logistical barriers remain due to inefficient services, inadequate human capacity, resource limitations, and political and social disruptions. Also, maintaining lifelong ART adherence will continue to be a major challenge. The continued development of ARV resistance will necessitate the development of new ARVs. The need for new, more expensive drugs will strain resources for ART programs, especially in resource-limited settings with a high disease burden.

In 2031, ART prophylaxis for HIV-uninfected persons will have been integrated into a package of HIV prevention modalities including structural and behavioral interventions, condom use, STD management (including the suppression or elimination of HSV infection), substitution therapy for drug users and access to clean injection equipment for injection drug users. Safe and effective combination ART will be used for prophylaxis. The use of triple-drug prophylaxis with drugs from different classes will decrease the probability of infection with HIV resistant viruses. A current example is the addition of maraviroc, a CCR5 blocking agent, with tenofovir and emtricitibine, nucleoside reverse transcriptase inhibitors. By 2031, more than a decade of experience with prophylactic
ART will have resulted in optimal practices for the various populations at highest risk for HIV infection. Intermittent, exposure-related ART will be the norm. For the highest risk people ART will be administered in a long-acting formulation by injection or an implantable device, and in women in combination with injectable hormonal contraception. ART for prevention will also be provided in vaginal rings that are placed over the cervix. ART suppositories will be used to reduce transmission via receptive anal sex.

Avoiding behavioral enhancement will be an ongoing challenge, requiring sustained education programs for HIV-uninfected persons on ART. The promotion of condom use for at-risk exposures will remain a key element of HIV prevention and counseling interventions will work to avoid a migration away from condom use. The protective efficacy of prophylactic ART and programmatic coverage will be the key factors in achieving a high level of HIV prevention impact. If efficacy is >90%, behavioral enhancement will not be a major problem for HIV transmission. However, the prevention of other STD transmission and unwanted pregnancies will require some combination of barrier protection, prophylaxis and contraception.

In areas where a large proportion of HIV-infected persons are on ART and prophylactic ART is available for high-risk persons, HIV transmission rates will decrease proportional to the ART coverage. This will result in very limited HIV transmission in settings with strong infrastructure and programs. In such settings, HIV will become sequestered among marginalized populations with limited access to services or adherence problems due to behavioral factors or substance abuse.

The relentless spread of HIV continues in countries that are unable to achieve a high level of ART coverage, whether for HIV-infected persons or for prophylaxis against HIV acquisition, due to resource-limitations, weak health systems, and political instability. A sustained, concerted global effort will be required to achieve the potential benefits afforded by ART - both for HIV treatment and for HIV prevention – for all populations.

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