Once upon a time there was a failed anti-cancer drug called zidovudine, which had been rejected because it was so toxic and had such unpleasant side effects. It sat on the shelf of a large pharmaceutical company. Twenty years later, under the name AZT, it became the vanguard of medicines in the fight against the human immunodeficiency virus (HIV).

In May 1984, shortly after the human immunodeficiency virus (HIV) had been unambiguously proved as the cause of AIDS, Samuel Broder and colleagues at the National Cancer Institute (NCI) initiated a program to develop therapies for HIV/AIDS. Using a CD4+ cell line that they had made, they developed an assay to screen drugs for their ability to protect CD4+ T cells from being killed by HIV.

Scientists at Burroughs-Wellcome found compounds that worked against certain mouse viruses. One compound that they were working with (AZT), which they had given the code name "BW A509X", was tested and demonstrated remarkable efficacy against certain mouse viruses. However, the scientists at Burroughs-Wellcome were not working with HIV themselves, and sent 11 compounds to the NCI team for testing against HIV in their newly developed assay. In February 1985, the NCI scientists found that BW A509X, one of these compounds, had potent efficacy in vitro and in rodents.

In an article, AZT's Inhuman Cost (NYT, Aug ’89) “…at $8,000/yr, AZT is said to be the most expensive prescription drug in history.”
In 1991 another antiretroviral, ddI (didanosine, Videx), created specifically for patients who had become resistant to AZT, was registered. In 1992 ddC (zalcitabine, Hivid), was approved for use in the US, followed by d4T (Zerit) in 1994 and 3TC (Epivir, lamivudine) in 1995. All these drugs are classified as nucleoside reverse transcriptase inhibitors (NRTIs)—same class drugs often show cross-resistance. In 1997 the FDA registered Combivir, a combination drug containing both AZT and 3TC. 1996 - nevirapine (Viramune, NVP), the first of the non-nucleoside transcriptase inhibitors (NNRTI)—stops the duplication of viral DNA by directly disabling the reverse transcriptase enzyme itself. Dual therapy - using two drugs simultaneously - was most effective when the drugs were from two different groups. Third class of drugs - protease inhibitors (PIs)—1995. These work at a later stage of the HIV life cycle by interfering with the protease enzyme, the other key enzyme required by the HI virus for intracellular replication.
With three groups of anti-HIV drugs available, HAART - highly active antiretroviral therapy, using multiple drugs - began to evolve, and anti-retrovirals became known as Lazarus drugs because they appeared to resurrect patients from near death.
### Classes of Antiretroviral Drugs

**Nucleoside Reverse Transcriptase Inhibitors (NRTIs)** NRTIs are DNA chain terminators that compete with endogenous deoxy-nucleotide triphosphates (dNTP) for incorporation into a growing viral DNA chain where they cause chain termination. NRTIs are pro-drugs that must be converted to their triphosphate forms by host cellular enzymes. The NRTIs have a low genetic barrier to resistance. First class approved by the FDA.

**Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)** The NNRTIs inhibit HIV-1 reverse transcriptase allosterically by binding to a hydrophobic pocket close to, but not contiguous with, the reverse transcriptase active site. Nearly all of the NNRTI resistance mutations are within or adjacent to this NNRTI-binding pocket.

**Protease Inhibitors (PIs)** The PIs are competitive active site inhibitors of HIV-1 protease that prevent the enzyme from processing the Gag and Gag/Pol polyprotein precursors necessary for viral maturation. Ritonavir is used solely at sub-therapeutic doses to inhibit cytochrome P450 (CYP)3A, to ‘boost’ the levels of other PIs.

The requirement for one or more major and one or more accessory PI-resistance mutations in combination with Gag cleavage site mutations explains the high genetic barrier for ritonavir-boosted PIs. PI-resistance mutations rarely emerge in patients receiving first-line therapy with a boosted PI. Resistant strains are found in pre-ART patients treated with nucleoside therapy and un-boosted first-generation PIs.

**HIV integrase strand transfer inhibitors (INIs)** Following reverse transcription, integrase cleaves conserved dinucleotides from the 3’ ends of double-stranded HIV-1 DNA, leaving dinucleotide overhangs on both ends of the genome (‘the 3’-processing reaction’). Integrase remains bound to each of the 3’ ends, circularizing the virus, and translocating it to the nucleus.

Catalyzes integration of viral double-stranded DNA into the host chromosome. Compounds that specifically inhibit strand transfer have been effective INIs.
**Entry Inhibitors - CCR5 co-receptor antagonist** The small-molecule inhibitor maraviroc allosterically inhibits the binding of HIV-1 gp120 to the host CCR5 (R5) co-receptor.

The most common reason for maraviroc failure is the presence of undetected minority variant CXC chemokine receptor 4 (CXCR4 or X4) tropic viruses.

Although HIV-1 can also develop maraviroc resistance via mutations that allow HIV-1 gp120 to bind to an inhibitor-bound R5 receptor, reports of such resistance have been documented primarily in vitro and in only a small number of clinical viruses.

More than 80% of patients are initially infected with HIV-1 viruses that are solely R5 tropic. X4 tropic viruses usually emerge in the later stages of HIV-1 infection. About 50% of patients chronically infected with HIV-1 are eventually found to harbour X4 tropic viruses.

**Fusion Inhibitors** Enfuvirtide, the only approved fusion inhibitor, inhibits the interaction of gp41 hairpin formation, the process by which two complementary parts of gp41 fold onto one another, shortening the protein and bringing the viral and host cell membranes together.

Despite its high potency and unique mechanism of action, enfuvirtide use is limited because it is administered subcutaneously, and frequently elicits painful injection site reactions. With the approvals of raltegravir and maraviroc, enfuvirtide use has decreased and it has been reserved for the most highly treatment-experienced patients.

Enfuvirtide has a low genetic barrier, and resistance develops rapidly in salvage therapy patients not receiving a sufficient number of additional active drugs.

**Ritonavir**’s (subtherapeutic) inhibition of the cytochrome P-450 CYP3A4 enzyme reduces the metabolism of concomitantly administered protease inhibitors and changes their pharmacokinetic parameters, including area under the curve (AUC), maximum concentration ($C_{\text{max}}$), minimum concentration ($C_{\text{min}}$) and half-life ($t_{1/2}$).
- HIV-1 has a high mutation rate, accumulating nearly one nucleotide mutation per replication cycle.
- $10^{10}$ virions are produced each day in untreated individuals.
- High recombination rate that occurs whenever more than one viral variant infects the same cell.
- HIV-1 variants with reduced susceptibility to any one or two drugs will often preexist in the viral quasispecies before initiating therapy.
- Drug resistance can either be acquired through drug selection pressure (acquired resistance), or transmitted from person to person (transmitted resistance).
- HIV-1 drug-resistance mutations almost without exception, decrease viral replication fitness.
- No cross-resistance between drug classes.
- NRTI and NNRTIs show synergism.
- Most ARV-resistance mutations decrease susceptibility to one or more ARVs of the same class.
- As drug-resistant mutations usually reduce viral fitness, most transmitted drug-resistant viruses revert to wild type gradually over a period of several years.

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<thead>
<tr>
<th>Generic name</th>
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<td>Abacavir</td>
<td>ABC</td>
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<td>Didanosine</td>
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<td>Tenofovir</td>
<td>TDF</td>
<td>Viread®</td>
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<tr>
<td>Zidovudine</td>
<td>AZT, ZDV</td>
<td>Retrovir®</td>
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- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

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<td>ETR</td>
<td>Intelec®</td>
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<td>Nevirapine</td>
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<td>Nevirapine extended release</td>
<td>NVP XR</td>
<td>Viramune® XR™</td>
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<tr>
<td>Rilpivirine</td>
<td>RPV</td>
<td>Edurant®</td>
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- Protease inhibitors (PIs)

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<td>Darunavir</td>
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<td>IDV</td>
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<td>Nelfinavir</td>
<td>NFV</td>
<td>Viracept®</td>
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<td>Ritonavir</td>
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<td>Norvir®</td>
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<td>Saquinavir hard gel caps</td>
<td>SQV</td>
<td>Inivirase®</td>
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<tr>
<td>Tipranavir</td>
<td>TPV</td>
<td>Aplivus®</td>
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- Integrase inhibitors (INIs)

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<td>CCR5 antagonist</td>
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<td>Maraviroc</td>
<td>MVC</td>
<td>Salzentry®</td>
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<tr>
<td>Fusion inhibitor</td>
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<tr>
<td>Enfuvirtide (T20)</td>
<td>ENF</td>
<td>Fuzeon®</td>
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</table>

| Mathematical modeling studies have suggested that any combinations in which at least three mutations are required should provide durable inhibition |
Why do we have soooo many anti-retroviral drugs?

**AIDS drugs are super attractive to drug companies:**
- Drugs are very expensive (in other words, Pharma can charge a lot for drugs that you need to stay alive)
- Patients often privately insured
- Government pays for drugs for many people
- Drugs don’t cure anybody
- Necessary for a lifetime
- Costs between $12,000-$20,000/year
- According to HHS, 60% of those who need ARV receive it

**Profits** for Glaxo Wellcome
- 1999, $589 million on Combivir (AZT + 3TC)
- 1997-2000, $800 million (AZT), $1.4 billion (3TC), $400 million (ddl), $1.4 billion (d4T)

Total markets in America and the five biggest European markets had an estimated **$13.3** billion in ARV sales in 2011
Combination therapy using three antiretroviral agents directed against at least two distinct molecular targets is the underlying basis for forestalling the evolution of drug resistance
There is essentially no cross-resistance between drug classes. Even viruses with high levels of resistance to drugs in one ARV class are fully susceptible to drugs belonging to a previously unused ARV class. In the case of the NRTIs and NNRTIs, both of which inhibit reverse transcriptase, there is often in vitro synergism, in that NRTI-resistant viruses often increase NNRTI susceptibility and NNRTI-resistant viruses occasionally increase NRTI susceptibility.

In contrast, there are often high levels of cross-resistance within each of the drug classes. Most ARV-resistance mutations decrease susceptibility to one or more ARVs of the same class. However, a few drug-resistance mutations have been shown to increase susceptibility to other ARVs of the same class. For some ARVs, multiple drug-resistance mutations are required to cause decreased susceptibility, while others require just a single mutation. The number of mutations necessary to confer resistance, and the ease or frequency at which the mutation develops, contributes to the ‘genetic barrier to resistance’ of the ARV. ARVs may differ greatly in their antiviral potency – the extent to which they decrease plasma HIV-1 RNA levels.

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Phenotypic susceptibility tests measure viral replication in cell culture in the presence of serial ARV dilutions. Plotting the inhibition of viral replication at increasing ARV concentrations creates a sigmoidal dose-response curve that is usually summarized by the ARV concentration that inhibits viral replication by 50% (IC$_{50}$).
The fitness of the wild-type virus ($R_0$, blue line) decreases with increasing drug concentration. A drug-resistant strain ($R'_0$, red line) is less fit than the wild type at low concentrations but more fit at higher concentrations. MSW is the range of concentrations where a resistant mutant, if present, will grow faster than the wild type and still has $R'_0 > 1$. WGW is the range of low concentrations where the wild type has $R_0 > 1$.

MSW = mutant selection window
WGW = wildtype growth window

As drug concentrations decay after the last dose is taken, the viral fitness passes through four different selection ranges. Depending on the drug, dose level and mutation, not all of these ranges may exist. The time spent in each selection window is also determined by the drug half-life. WT, wild type.

The most common side effects of ritonavir therapy are:
asthenia, malaise
diarrhea
nausea and vomiting
abdominal pain
dizziness
insomnia
sweating
taste abnormality
metabolic
hypercholesterolemia
hypertriglyceridemia
elevated transaminases
elevated CPK
One of ritonavir's side effects is hyperglycemia. It appears that ritonavir directly inhibits the GLUT4 insulin-regulated transporter, keeping glucose from entering fat and muscle cells. This can lead to insulin resistance and cause problems for Type Ⅱ diabetics.
(1) high throughput compound screens with virus-specific replication or enzymatic assays, (2) optimization of inhibitors using lead compounds based on homologous enzymes or targets, and/or (3) rational drug design modeled on the structures of viral proteins.
Trends in Annual Age-Adjusted* Rate of Death Due to HIV Infection by Sex, United States, 1987–2009
In 2005, the media hyped the discovery of a "superstrain" of HIV, which allegedly progressed to AIDS in a matter of months, and was impervious to drug treatment. The truth is a bit more complicated. A patient, who had reported multiple unprotected sexual encounters with gay men, was diagnosed at New York’s Aaron Diamond AIDS Research Center with three-drug-class-resistant HIV (3DCRHIV). His virus was resistant to two kinds of reverse transcriptase inhibitors and protease inhibitors. Because it was so difficult to treat, his infection progressed quickly to AIDS.

Scientists interviewed for FRONTLINE said the superstrain fear-mongering was overblown, but that multidrug-resistant viruses are beginning to be a problem. If two people with different strains of HIV infect each other again, the viruses can recombine, and increase the chances of both viruses becoming multidrug resistant. When people acquire drug-resistant strains of HIV, their treatment options are limited from the beginning

_This is different from multi-drug antibiotic resistant bacterial mutants, why?_

What is "salvage therapy"?

When a patient nears the end of his or her available drug options, it means the virus in that person's body is resistant to several different drug classes. As a last option, known as "salvage therapy," doctors may use whatever drugs still have an impact on the virus, even if they offer only a small benefit. Some individuals who have been taking the drugs since they became available in 1996 are reaching the end of their options and more and more will end up on salvage therapy in the coming years if new drugs don't become available. In the United States, where antiretrovirals have been available longer than anywhere else, an estimated 40,000 people with AIDS no longer respond to treatment.
**Genotypic resistance** testing relies on detecting known drug-resistance mutations in the enzymatic targets of antiviral therapy: protease, reverse transcriptase, and, if specially requested, integrase and glycoprotein (gp)41

Many variants in a viral mixture

Genotypic more sensitive to pick these out than phenotypic

**There are two mechanisms of NRTI resistance:** (i) discriminatory mutations that enable the reverse transcriptase to discriminate between dideoxy-NRTI chain terminators and the cell’s naturally produced dNTPs, thus preventing NRTIs from being incorporated into a growing viral DNA chain; and (ii) primer unblocking mutations that facilitate the phosphorylytic excision of an NRTI-triphosphate that has been added to the growing viral DNA chain

The principles of salvage therapy for patients for whom more than one regimen has failed are similar to those for patients for whom a single regimen has failed: the salvage regimen should be sufficiently potent to suppress virus levels to below the level of detection, and should have a sufficiently high genetic barrier to resistance to prevent virological rebound

As of 2009, 30-50% of those in therapy were in salvage therapy. Not too effective, deaths due to AIDS are again increasing. 15% in Salvage therapy die within 3 years.
• Plasma HIV viremia can be suppressed and maintained below the limits of detection for prolonged periods of time using ART.
• ART alone cannot eradicate HIV
• Persistence of viral reservoirs in the peripheral blood and lymphoid tissues

• Three independent studies in which the persistence of a small but detectable pool of latently infected, resting CD4+ T cells carrying replication-competent virus was documented in virtually all study patients who had received clinically effective ART for up to 3 years

• Rapid viral rebound shortly after discontinuation of therapy in infected individuals in whom profound and sustained suppression of plasma viremia had been achieved for prolonged periods
the total body burden of the latent viral reservoir was very small (fewer than 10 million cells per infected person).

Latently infected, resting CD4+ T cells exhibited primarily a memory phenotype.

possibility that early initiation of ART may prevent the generation of viral latency?

**Acute/Early phase:** half-life of the latent viral reservoir was approximately 4–6 months—studies projected that it would require at least 7–8 years of continuous therapy to eradicate HIV using the assumptions that ART was 100% effective at suppressing viral replication and that no other viral reservoirs existed in vivo.

**Chronic Phase:** half-life of 44 months, 60 years to clear!
Drug-Protease inhibitors Can Have Terrible Side-Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side-Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atazanavir</strong></td>
<td>Hyperbilirubinemia, Jaundice, liver function</td>
</tr>
<tr>
<td><strong>Darunavir</strong></td>
<td>Rash, liver function</td>
</tr>
<tr>
<td><strong>Fosamprenavir</strong></td>
<td>Diarrhea, Nausea, Vomiting, liver function</td>
</tr>
<tr>
<td><strong>Indinavir</strong></td>
<td>Nephrolithiasis, flank pain, Hyperbilirubinemia, Hyperlipidemia, Alopecia, dry skin, ingrown nails, Insomnia</td>
</tr>
<tr>
<td><strong>Lopinavir/ ritonavir</strong></td>
<td>Diarrhea, nausea, vomiting, Dyslipidemia</td>
</tr>
<tr>
<td><strong>Nelfinavir</strong></td>
<td>Diarrhea (common), Nausea, vomiting, liver function tests</td>
</tr>
<tr>
<td><strong>Ritonavir</strong></td>
<td>Nausea, vomitting, diarrhea, abdominal pain, Fatigue, fatique, peripheral numbness, taste pervasion</td>
</tr>
<tr>
<td><strong>Saquinavir</strong></td>
<td>Nausea, vomiting, Oral ulcerations, diarrhea, liver function</td>
</tr>
<tr>
<td><strong>Tipranavir</strong></td>
<td>Nausea, vomiting, diarrhea, liver function, Increased cholesterol and triglycerides, Rash, Intracranial hemorrhage</td>
</tr>
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</table>
This section starts with an overview of the number of patients on ARVs and the total ARV market size in 2011. We then discuss the global funding outlook and present the forecasted trends for key ARVs over the next five years. More details are provided on pediatric and PMTCT programs in this report versus previous Market Reports given the significant changes in funding and other key trends affecting the pediatric space.

We focus primarily on the generic-accessible market, for which the most robust data is available. Where possible, we also add insight into the generic-inaccessible market based on publicly available data. An overview of the CHAI analyses and methodologies used in this section is provided in Appendix D.

### Market Review

#### Number of patients on ART grew by 24% in 2011 vs. 2010

Over the past five years, there has been a significant increase in access to ARV treatment. Between 2006 and 2011, the number of patients on therapy grew from 2 million to 8 million. Of those, 1.5 million were placed on treatment between 2010 and 2011 alone, despite global concerns about limited funding. This represents a 24% growth in patients on ARV treatment between 2010 and 2011.

Coverage of eligible patients, both adults and children, also increased in recent years (see Exhibit 1.1), growing from 28% in 2008 to 54% in 2011. Scale-up is expected to continue increasing over the next 5 years, to an estimated 67% coverage in 2016.

#### Market size of generic-accessible market expanded in 2011

In generic-accessible countries, the market size for ARVs grew from an estimated $853 million in 2010 to $1,008 million in 2011, an increase of 18%. Market growth was higher than the 2009-2010 period (10%), despite significant price reductions achieved in South Africa's 2010 tender. South Africa (RSA) represents 24% of the generic-accessible market and achieved 20-60% reduction in the price of key ARVs; this resulted in RSA's market size decreasing from $292 million in 2010 to $247 million in 2011 (despite a 0.3 million increase in patients on treatment). If South Africa is excluded, the market size in generic-accessible countries increased by 36% (see Exhibit 1.2).

Adult first-line ARVs accounted for 82% of the total dollar value of the ARV market in generic-accessible countries. Following the demotion of stavudine (d4T) in the 2010 WHO Guidelines, there has been a shift away from d4T towards the more expensive tenofovir (TDF) or zidovudine (AZT) based regimens in 2011. (Please refer to the Market Outlook section for more detail on NRTI.)

---

**EXHIBIT 1.1: PATIENT TREATMENT COVERAGE IN LOW AND MIDDLE INCOME COUNTRIES**

![Graph showing patient treatment coverage from 2003 to 2011 for CD4 < 200 and CD4 < 350](image-url)
Overall side-effects of multi-drug therapy include:

Heart problems
Bone loss
Lactic acidosis
Liver and kidney dysfunction
Mitochondriosis (lipodystrophy, fatigue, shortness of breath, weight loss, rapid heartbeat, alopecia, numbness, pain in extremities, inflammation of the pancreas, etc.

Also found gynomastia, protease paunch, buffalo hump

Before HIV infection, 32 year old women reported bra size, 34C. Patient complained of a progressive swelling of the breasts and her chest circumference progressively increased 95 cm (baseline measurement) to 110 cm. A slight increase in abdominal girth and wasting of the buttocks and lower limbs also appeared, but her body weight remained unchanged.

Cortisol, adrenocorticotropic hormone, growth hormone, C-peptide and testosterone, triglycerides (75 mg/dL), cholesterol (180 mg/dL), and glucose (83 mg/dL) -- normal. Her CD4 count was 400 cells per microliter and viral load 2800 copies/per milliliter.

During the next 12 months, the patient presented with further enlargement of the breasts, reaching a total increase of five bra sizes (chest circumference increased to 118 cm)--
Her CD4 count increased to 545 cells per microliter and the viral load become undetectable (<80 copies per milliliter).

AIDS PATIENT CARE and STDs Volume 16, Number 7, 2002
Post-exposure prophylaxis (PEP): PEP involves taking a short course of ARV drugs, usually for a month, after a high-risk exposure. To be most effective, PEP should be started immediately after possible exposure, waiting no more than 72 hours.

If you suspect a high-risk exposure to HIV—sperm leaking out of a condom during intercourse with an HIV-positive insertive partner; receptive anal sex without a condom with a partner who is either HIV positive or whose status you do not know (WTF?) or you have shared drug-injection works with someone who is either HIV positive or whose status you do not know (really WTF??)—contact your health care provider or local hospital emergency room as soon as possible.

Pre-exposure prophylaxis (PrEP):
PrEP involves having an uninfected person take ARV drugs—usually Truvada* (tenofovir plus emtricitabine)—before, during and after possible high-risk exposures to reduce the risk of becoming infected with HIV.

Based on the results of clinical trials the FDA has approved Truvada as PrEP, with the requirement that it be used every day, even during periods of minimal or low-risk sexual activity.

Future studies may explore intermittent dosing strategies (e.g., using PrEP only during periods of high-risk sexual or drug-using activity).

Seems like it would be easier not to share needles or engage in unprotected sex???

*TRUVADA (emtricitabine/tenofovir disoproxil fumarate) nucleoside inhibitors
**Treatment-as-prevention:**
Whereas PrEP focuses on prescribing ARVs to people who aren't infected with HIV to help them remain free of the virus, treatment-as-prevention (TasP) involves prescribing ARVs to those who are infected with HIV in order to reduce the amount of virus in their blood (and genital fluids) so that they are less likely to infect others.

One clinical trial, initially reported at a conference in July 2011, suggested TasP may be effective. The study, HIV Prevention Trials Network (HPTN 052) demonstrated that the use of ARVs by HIV-positive heterosexual men and women cut the chance that their HIV negative partner would become infected by roughly 96 percent.

**Vaginal and Rectal Microbicides:** Microbicides are an emerging technology designed to allow at-risk HIV-negative women and men to protect themselves from HIV. A microbicide has not yet been approved for this purpose (because they don’t WORK!)
Finding a permanent cure

- Use of aggressive drug regimens (DOES NOT WORK)
- Use of virus purging agents
- Use of HIV-specific killing agents
- Early initiation of antiretroviral therapy
- Enhancement of anti-HIV immunity
- Better understanding of HIV basic science (MIGHT WORK)
- Modification of host genetics
Each finger recognizes 3–4 base pairs of DNA via a single α-helix and several fingers can be linked in tandem to recognize a broad spectrum of DNA sequences with high specificity. This can be coupled to the nonspecific DNA cleavage domain of the Type II S restriction enzyme, FokI, to produce a zinc-finger nuclease (ZFN).

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human CD4+ T cells stimulated with anti-CD3/anti-CD28 coated magnetic beads, CCR5 is downregulated causing transient resistance to R5 HIV
Our studies provide a fundamental demonstration that inactivation of cxcr4 by treatment with X4-ZFNs rendered human CD4+ T cells resistant to infection by X4 virus strains, while CXCR4 inactivation in the context of a ccr5Δ32 homozygous background rendered cells resistant to infection by both R5 and R5X4 strains.
Treatment with X4-ZFNs is effective in ccr5Δ32 homozygous human CD4+ T cells

Mock HIV

Primary X4 HIV: Bk132

Lab-adapted X4 HIV: HxB2

Primary R5X4 HIV: R3A

Cumulative live cell count (x 10⁶)

Days post stimulation
SB-728 Ad5/35, CCR5 ZFNs

apheresis enrich CD4+

G-CSF mobilize, apheresis, CD34+ purify

HSC, preclinical development

CD4+ T cells, phase I trial

expand cryopreserve test

ENDPOINTS safety CD4/HIV levels CCR5 selection

chemotherapy

infuse

cryopreserve test

infuse
HIV gene engineering approaches using Zinc-finger directed mutations

Knockout CCR5 AND CXCR4 in T cells

Altering cell death pathways
Cell Death Dis. 2013 Jul 11;4:e7182013.248

Excision of HIV-1 proviral DNA
Nucleic Acids Res. 2013 Sep;41(16):7771-82

Editing of CCR5 in bone marrow stem cells
Mol Ther. 2013 Jun;21(6):1259-69

Other engineering approaches

Zinc finger nucleases

TAL effector nucleases, or TALENs

CRISPR (clustered regularly interspaced short palindromic repeats)