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# Current status and prospects of HIV treatment

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Current antiviral treatments can reduce HIV-associated morbidity, prolong survival, and prevent HIV transmission. Combination antiretroviral therapy (cART) containing preferably three active drugs from two or more classes is required for durable virologic suppression. Regimen selection is based on virologic efficacy, potential for adverse effects, pill burden and dosing frequency, drug–drug interaction potential, resistance test results, comorbid conditions, social status, and cost. With prolonged virologic suppression, improved clinical outcomes, and longer survival, patients will be exposed to antiretroviral agents for decades. Therefore, maximizing the safety and tolerability of cART is a high priority. Emergence of resistance and/or lack of tolerability in individual patients require availability of a range of treatment options. Development of new drugs is focused on improving safety (e.g. tenofovir alafenamide) and/or resistance profile (e.g. doravirine) within the existing drug classes, combination therapies with improved adherence (e.g. single-tablet regimens), novel mechanisms of action (e.g. attachment inhibitors, maturation inhibitors, broadly neutralizing antibodies), and treatment simplification with infrequent dosing (e.g. long-acting injectables). In parallel with cART innovations, research and development efforts focused on agents that target persistent HIV reservoirs may lead to prolonged drug-free remission and HIV cure.

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## Introduction

Since the approval of zidovudine (AZT) in 1987, over 25 antiretroviral agents in six mechanistic classes have been approved to treat HIV infection (Figure 1). Combination antiretroviral therapy (cART) is the treatment paradigm established in the late 1990s responsible for the dramatic decline in AIDS deaths and is composed of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus a third active drug from a different class. Contemporary HIV treatment is highly effective at suppressing plasma viremia, and significant progress has been made toward regimen simplification through the combination of three active drugs into single-tablet regimens (STRs) (Figure 1) and optimization of drug profiles that maximize long-term tolerability and safety. Lifelong, chronic therapy without treatment interruption is the standard of care, and the availability of multiple effective drugs in several classes with differing resistance, safety, and tolerability profiles provides choices after failure of first-line treatment.

Herein, we review the current status of antiretroviral therapy and guidelines for HIV-infected adults, as well as prospects for further innovation in HIV treatment to benefit patients and optimize their long-term health.

## Goals of antiretroviral therapy

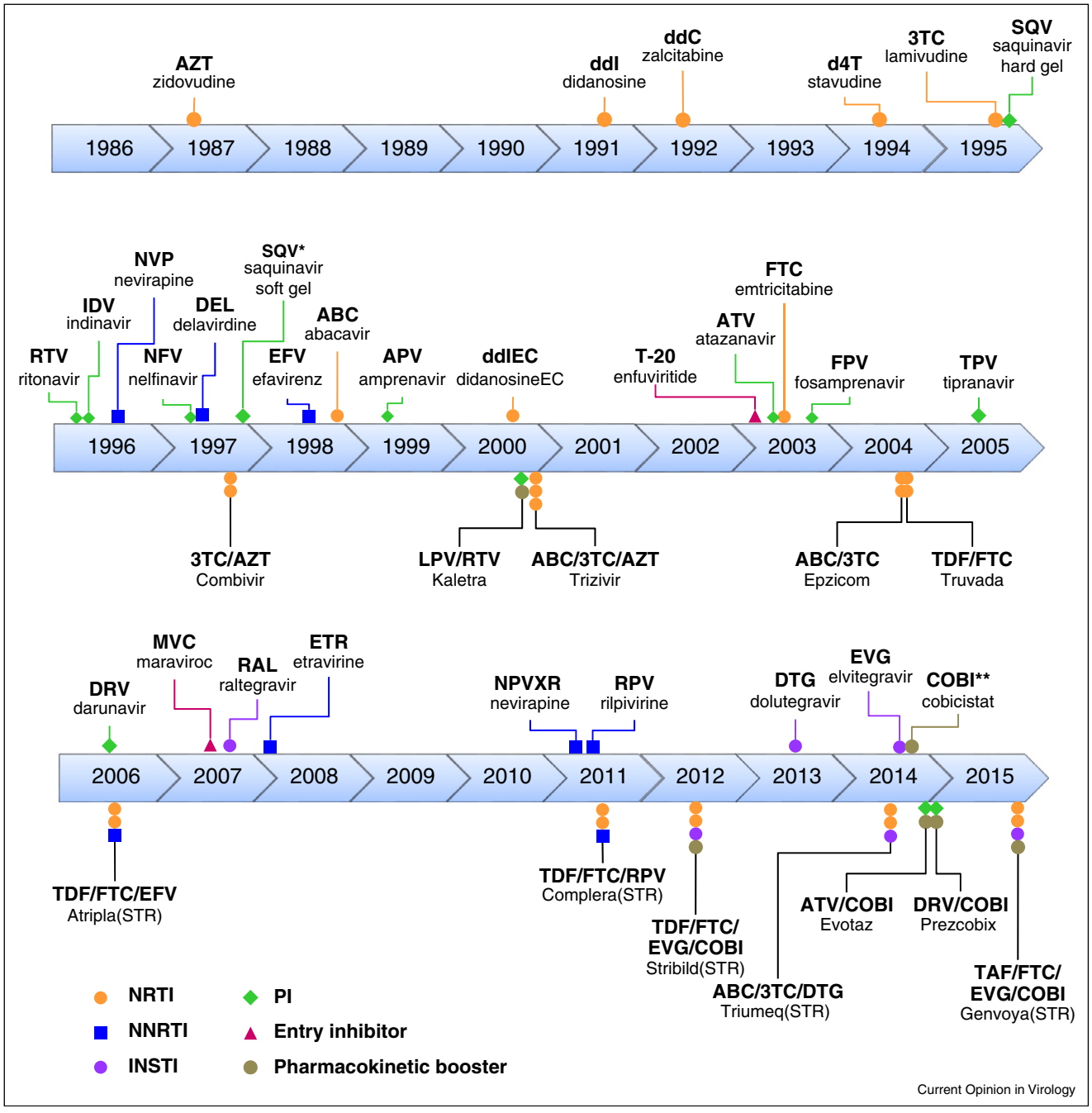
Eradication of HIV cannot be achieved with current cART due to the pool of latently infected CD4 T cells established early during acute infection. However, cART can reduce HIV-associated morbidity, prolong survival, and prevent HIV transmission [1–4]. Maximal and durable suppression of plasma viremia restores and preserves immunologic function, delays or prevents the development of drug-resistant mutations, and may also decrease the immune activation and inflammation thought to contribute to end-organ damage [5–7]. Suppressing plasma viremia below detection limits is possible within weeks of therapy and depends on adherence to an efficacious regimen.

Morbidity and mortality in HIV-infected subjects is increasingly driven by non-AIDS associated comorbidities such as kidney, liver, and heart disease [8,9] (Linley L *et al.*, Abstract B08-1, 2007 National HIV Prevention Conference, Atlanta, GA, December 2007). Even with cART, aging patient populations with HIV-1 infection experience more age-related comorbidities, such as diabetes, and cardiovascular, renal, and bone disease, which manifest earlier than in HIV-uninfected peers [10•]. With prolonged virologic suppression, improved clinical outcomes, and longer survival, patients may be exposed to antiretroviral agents for decades [11•]. Thus, maximizing the safety and tolerability of cART regimens while maintaining strong clinical efficacy is a high priority.

## Guidelines and preferred regimens for first-line therapy

Therapy used to be initiated based on decreasing CD4 cell count or clinical evidence of AIDS. More recently, therapy is being initiated regardless of the CD4 cell count, often immediately after a patient's diagnosis, a

**Figure 1**




FDA-approved individual antiretroviral drugs and drug combinations. *Saquinavir soft gel (Fortovase) is no longer marketed. **COBI has no antiretroviral activity; COBI is a pharmacokinetic enhancer that is used to increase (boost) the systemic exposure of EVG and protease inhibitors; COBI is co-formulated in fixed dose combinations with ATV or DRV. ER, enteric-coated; XR, extended release; STR, single-tablet regimen.

clinical decision in part facilitated by the improved tolerability and safety of contemporary cART drugs. Antiretroviral regimens that contain at least two and preferably three active drugs from two or more classes are recommended for virologic suppression. Initial therapy generally consists of two NRTIs combined with a third agent such as an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a pharmacologically boosted protease inhibitor (PI). Global and regional guidelines have generally consistent recommendations for first-line therapy (Table 1); US and European guidelines have begun to