Initiating Therapy: When to Start, What to Use

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Decisions regarding whether to start combination antiretroviral therapy (cART) during primary infection and when to initiate treatment during chronic infection continue to evolve. Although current data suggest that there may be a benefit to therapy during primary infection, results are inconclusive. Once begun, treatment probably should be continued indefinitely, since its potential advantages disappear over time if treatment is stopped. Recent studies suggest that cART may be useful at higher CD4 cell count thresholds than are currently recommended in several guidelines. Several regimens are acceptable as initial therapy, with tenofovir/emtricitabine/efavirenz favored by many because of potency and ease of administration. Other favored regimens include combinations of 2 nucleoside (or nucleotide) reverse-transcriptase inhibitors and a ritonavir-boosted protease inhibitor. Some new antiretroviral drugs under study, particularly integrase inhibitors, may prove useful in treatment-naive patients.

Recommendations about when to initiate combination antiretroviral therapy (cART) and what to use for treatment-naive patients are constantly evolving. The CD4 cell count at which therapy is begun and the initial regimen used may have a significant impact on survival, health, and quality of life. This article summarizes recent reports regarding when to begin cART and which regimens to use. It also describes certain investigational antiretroviral agents (ARVs) that could influence future initial treatment options.

WHEN TO START

It has been clearly established that HIV-infected patients with CD4 cell counts \( \leq 200 \) cells/\( \mu L \) and those with symptoms or signs of active, established HIV infection should begin cART [1, 2]. Debate continues about whether to start treatment during primary/acute infection and when to treat chronic asymptomatic infection if CD4 cell counts are \( > 200 \) cells/\( \mu L \). Studies to date suggest that it may be reasonable to start treatment during acute primary infection, although evidence does not conclusively support long-term benefits of this approach. There are, however, several studies that support raising the CD4 cell count threshold for initiating treatment of chronic asymptomatic infection, to \( \approx 350 \) cells/\( \mu L \) or even to \( \approx 500 \) cells/\( \mu L \).

Primary Infection

Reasons advanced for starting cART during acute primary HIV infection include decreasing virus transmission, limiting viral evolution and resistance risk, establishing a lower viral set point, and preserving HIV-specific immune responses. Studies in the developed and developing world support an elevated risk of transmission during early-stage infection. Phylogenetic analysis of all genotyped early-stage infections (i.e., \(< 6 \) months after seroconversion) from the Quebec Primary HIV Infection cohort demonstrated that 49% of virus strains formed phylogenetic clusters, suggesting that different infections may vary in transmissibility and supporting a major role for early-stage infection in transmission [3]. Evaluation of HIV-discordant, monogamous couples in Uganda (\( N = 235 \)) also concluded that transmission risk during acute and early-stage infection was nearly 12-fold higher than that during chronic infection [4].

High-level viremia during early-stage infection prob-
ably accounts for much of this elevated transmission risk. Acute/early-stage HIV infections are characterized by extremely high viral loads (VLs) that sometimes exceed 1 million HIV RNA copies/mL in blood and genital secretions [5], and high VL predicted greater risk of transmission in the Uganda study [4]. In addition, acute/early-stage infections often are undiagnosed and may be accompanied by high-risk behaviors (i.e., unprotected sex), which may facilitate transmission.

As a public health measure, some have suggested initiation of cART early during infection, to reduce VL and lower transmission risk [6]. Starting cART during acute infection (i.e., ≤2 weeks after seroconversion; n = 13) or early-stage infection (i.e., 2 weeks to 6 months after seroconversion; n = 45) and treating for a median of approximately 1.5 years has been associated with lower VLs (by ~0.5 log10 copies/mL [unadjusted]) 24 weeks after treatment cessation (n = 337 untreated patients) (P < .05 for difference between treated vs. untreated patients) [7]. However, virologic benefits did not persist after treatment discontinuation. At 72 weeks after treatment termination, differences in VLs remained significant only for the few patients who had received acute-phase therapy and only when data were adjusted for baseline VL and CD4 cell count.

The results of another, smaller investigation (N = 20) support these findings. Subjects who received acute-phase therapy for 24 weeks had suppressed VLs (<50 copies/mL) and increased CD4 cell counts, compared with untreated subjects (884 cells/µL vs. 533 cells/µL, respectively; P = .007), at the end of treatment. By 6 months after cART cessation, CD4 cell counts and VLs were similar for subjects in both groups [8].

Issues that have been raised against initiation of cART during acute infection include cost, increased potential for resistance and toxicity, and the likelihood of diminished adherence. Recent findings suggest less reason for these concerns (see the subsection “Addressing factors that favor delaying cART at CD4 cell counts ≥200 cells/µL”). However, data regarding the long-term effects of acute-phase therapy on morbidity and mortality are lacking.

The evidence is insufficient to conclusively support treatment during acute HIV infection, although many theoretical arguments can be made for doing so. If treatment is initiated during this period, it should be continued indefinitely to maintain its benefits.

**CD4 Cell Count ≥200 Cells/µL: Chronic Asymptomatic Infection**

Major guidelines currently recommend starting cART at CD4 cell counts ≤200 cells/µL but advise considering or offering treatment at CD4 cell counts of 201–349 cells/µL [1, 2]. Data from controlled trials are not available to support initiation of therapy at a higher CD4 cell count threshold. A major randomized trial addressing this issue may be difficult to perform for a variety of reasons, including the numbers of subjects required to show small differences, the length of time required to do such a study, the enormous cost required, and the inherent biases of both patients and physicians that might make enrollment and continued participation difficult. In addition, the landscape of HIV treatment changes so rapidly that the results of such a study may be irrelevant by the time the results are reported 5–10 years later. Decisions regarding the optimal CD4 cell count at which to initiate therapy will be more likely to draw on detailed analyses of cohort data from varied populations, although there are well-recognized problems of potential bias when nonrandomized data are used to make such decisions.

**Starting at CD4 cell counts ≈350 cells/µL or ≥500 cells/µL appears to improve survival.** A prospective, observational study compared mortality among patients who had started cART at specified CD4 cell count ranges with those who had deferred treatment. Starting cART at CD4 cell counts ≈350 cells/µL (i.e., 201–350 cells/µL; n = 340) was found to be associated with a reduced rate of death, compared with that for patients at the same CD4 cell count level who had deferred cART (n = 59; 15.4 vs. 56.4 deaths/1000 person-years, respectively; P < .001) [9]. A nonsignificant trend toward lower mortality when cART is started at CD4 cell counts ≥500 cells/µL (i.e., 351–500 cells/µL; n = 240 patients starting cART vs. n = 887 patients delaying cART; P = .17) led to speculation that follow-up for longer than the median 3–4 years in this study could have revealed a significant benefit for this group as well.

Among injection drug users (IDUs), beginning cART at CD4 cell counts ≥350 cells/µL raised the survival rate to approximately that of their HIV-seronegative counterparts. Among HIV-infected IDUs with CD4 cell counts >350 cells/µL, the mortality rate among those who did not receive cART (n = 222) was 44% higher than that among those who started cART (n = 99) [10]. Starting cART at CD4 cell counts ≈350 cells/µL (i.e., 200–350 cells/µL) did not raise the survival rate to that of HIV-seronegative IDUs (n = 947) and did not result in as dramatic an improvement in survival rate. The mortality rate among those with CD4 cell counts of 200–350 cells/µL who did not start cART (n = 159) was 15.7% higher than the mortality rate among those who started cART at that level (n = 87). Findings concerning the benefits of earlier therapy among IDUs are especially noteworthy because injection drug use has been associated with a reduced CD4 cell count response to cART [11].

**Starting at higher CD4 cell counts reduces the risk of progression to AIDS or death.** CD4 cell count at the start of therapy was the strongest of 5 prognostic factors for risk of death and AIDS in a model developed by the ART Cohort Collaboration [12]. This analysis evaluated data from 20,379 patients who were followed for <2 to >5 years and assessed the
among those who had started cART at CD4 cell counts less than or equal to 350 cells/µL, assumed transmission group (IDU or not), age, and the presence or absence of clinical AIDS. Other factors predicting increased risk of disease progression included likely transmission through injection drug use and an AIDS diagnosis. HIV RNA level at the start of cART did not predict death [12].

Other evidence suggesting clinical benefits to starting early. A major trial examining the impact of structured treatment interruption yielded additional information that may indirectly affect the decision about when to initiate cART. The Strategies for Management of Antiretroviral Therapy (SMART) study (N = 5472) reported that waiting to start cART until CD4 cell count was <250 cells/µL and stopping therapy at a CD4 cell count of 350 cells/µL were associated with an increased risk of death from any cause, as well as a higher risk for opportunistic infections and cardiovascular, renal, or hepatic disease [13].

Persons in the interrupted-therapy group of the SMART study received cART for 33.4% of the follow-up time, compared with 93.7% of the follow-up time for those assigned to receive continuous cART (mean follow-up, 16 months). The increased risk of non-HIV morbidity and mortality observed among persons who spent more time not receiving cART raises the possibility that these outcomes were related to prolonged periods of immunodeficiency while not receiving therapy. In support of this hypothesis, the hazard ratio (HR) for death from causes other than opportunistic infection fell when adjusted for most recent CD4 cell count and most recent HIV RNA level (unadjusted HR, 1.8 [95% confidence interval (CI), 1.1–2.9]; adjusted HR, 1.2 [95% CI, 0.7–2.2]).

Analysis of the HIV Outpatient Study (HOPS) cohort also indicated that starting cART at higher CD4 cell counts was associated with lower risks of death and opportunistic infection [14]. Beginning cART at CD4 cell counts \( \leq 200 \text{ cells/µL} \) also increased the risks of peripheral neuropathy, anemia, and renal insufficiency, whereas starting cART at higher CD4 cell counts appeared to reduce these risks [15].

Immunologic and virologic benefits of starting at CD4 cell counts \( \geq 350 \text{ cells/µL} \). Analysis of data from the Johns Hopkins HIV Clinical Cohort (N = 655; median observation period, 3.8 years) showed that baseline CD4 cell count predicted subsequent CD4 cell count responses [11]. After 6 years, CD4 cell counts had nearly normalized (median, 829 cells/µL) among those who had started cART at CD4 cell counts \( >350 \text{ cells/µL} \) (figure 1) [11]. In contrast, the median CD4 cell count was 493 cells/µL for patients with baseline CD4 cell counts \( \leq 200 \text{ cells/µL} \) and was 508 cells/µL for those with baseline CD4 cell counts of 201–350 cells/µL. CD4 cell counts increased by a median of 274 cells/µL from baseline in the entire population and reached a plateau after \( \sim 4 \) years of sustained viral suppression. These data suggest that starting early (at CD4 cell counts \( >350 \text{ cells/µL} \)) and maintaining therapy may be important to optimizing immunologic recovery.

Similar observations have been made by others. The EuroSIDA study group reported that those individuals starting cART at CD4 cell counts \( >350 \text{ cells/µL} \) approached the CD4 cell counts of uninfected individuals after \( \geq 3 \) years of therapy [16]. In addition, Gras et al. [17], using data from the AIDS Therapy Evaluation Project of the Netherlands (ATHENA), reported that individuals beginning cART at CD4 cell counts of 350–500 cells/µL were nearly 3 times more likely to achieve a “normal” CD4 cell count (800 cells/µL) within 7 years, compared with those starting cART at CD4 cell counts of 200–350 cells/µL (multivariate HR, 2.84 [95% CI, 2.45–3.28]; \( P < .0001 \)). Specifically, 46% of those with baseline CD4 cell counts of 200–350 cells/µL achieved CD4 cell counts of 800 cells/µL within 7 years, compared with 73% of those with baseline CD4 cell counts of 350–500 cells/µL. An earlier analysis of the HOPS cohort indicated that starting, rather than delaying, cART at a given CD4 cell count threshold also increased the probability of achieving undetectable plasma VLs (\( P = .009 \) for the difference at CD4 cell counts of 201–350 cells/µL; \( P = .03 \) for the difference at CD4 cell counts of 351–500 cells/µL) [9].

Other factors to consider in deciding when to start therapy. Although CD4 cell count often is the primary parameter to consider when deciding whether to initiate therapy, other information also may be helpful. A baseline VL \( \geq 100,000 \text{ copies/mL} \) has been associated with a higher risk of progression [18, 19]. Despite a recent report suggesting that baseline VL might explain only 4%–6% of the variability in CD4 cell count loss in 2 cohorts [20], VL remains an important measure in the prediction of clinical outcome [1]. Guidelines of both the International AIDS Society–USA Panel and the US Department of Health and Human Services suggest stronger consideration for starting cART at CD4 cell counts \( \leq 350 \text{ cells/µL} \) but at >200

![Figure 1. Median CD4 lymphocyte count over time, stratified by baseline CD4 cell count. Adapted from [11]. HAART, highly active antiretroviral therapy.](image-url)
cells/µL, if VL is >100,000 copies/mL [1, 2]. A rapidly declining CD4 cell count (i.e., >100 cells/µL/year) also is an argument for starting therapy at CD4 cell counts $\leq 350$ cells/µL [2].

CD4 cell percentage also may be considered when the decision to initiate cART is unclear. CD4 cell percentage at initiation predicted disease progression independent of absolute CD4 cell count in an observational study ($N = 1891$) [21]. Among patients initiating cART at CD4 cell counts of 200–350 cells/µL ($n = 417$), a CD4 cell percentage of <15% independently predicted an increased risk of death [22]. In such situations, CD4 cell percentage may predict outcomes by serving as a surrogate marker for immune activation. Older patients (>45 years of age), IDUs, and those coinfect with hepatitis C virus also should be considered for early therapy, since these risk factors may reduce CD4 cell count responses to cART [11, 23].

Addressing factors that favor delaying cART at CD4 cell counts $>200$ cells/µL. Certain objections to starting cART before CD4 cell counts are $\leq 200$ cells/µL have been raised, including an increased risk of drug toxicity, the development of increased antiviral drug resistance, and the likelihood of diminished adherence. Recent findings suggest that each of these factors may have a less-negative impact than once believed. Newer once- or twice-daily regimens are easier to follow than older regimens, which is likely to improve adherence. Moreover, newer regimens appear to be more “forgiving” than older regimens. Viral suppression to <400 copies/mL occurs at lower levels of adherence to certain currently popular regimens, compared with older regimens, as reported elsewhere [24, 25]. Adherence of >75% to a nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based regimen may be associated with a <10% rate of virologic failure, which is likely to be related to the inherent potency of such regimens, convenience, increased tolerability, and the long plasma half-life of these drugs [26].

The risk of resistance emergence is relatively low in persons starting therapy with current cART regimens. Among individuals receiving lopinavir/ritonavir (LPV/r)-based regimens, primary protease inhibitor (PI) resistance did not occur, and resistance to reverse-transcriptase inhibitor (RTI) components was uncommon [27]. Similarly, fosamprenavir (FPV)-associated resistance mutations developed in $\sim$1.5% of patients (5 of 74) experiencing virologic failure, over 48 weeks [28]. This finding is from a meta-analysis of 3 major trials of FPV with or without ritonavir boosting. In Gilead Study 903, resistance rates among patients receiving NNRTI-based therapy ranged from 2.7% (to tenofovir disoproxil fumarate [TDF]) to 8.3% (to efavirenz [EFV]). This 144-week, double-blind trial randomized patients to a regimen of TDF or stavudine (d4T) plus EFV and lamivudine (3TC) [29].

Preliminary findings suggest that initiating treatment at higher CD4 cell counts may reduce the risk of toxicity. Analysis of data from the HOPS cohort found that patients were less likely to develop renal insufficiency, lipoatrophy, and distal peripheral neuropathy when starting cART at progressively higher CD4 cell counts (200–349 cells/µL, 350–499 cells/µL, and $\geq 500$ cells/µL) [14].

Conclusions. Over the 2 decades since antiretroviral therapy has been with us, the pendulum of when to initiate therapy has swung back and forth because of the variability among regimens with respect to potency, toxicity, adherence, and resistance. As regimens have become more potent, less toxic, and more forgiving, the pendulum is likely to swing toward earlier initiation of therapy, to reduce the long-term adverse consequences of HIV infection. Whether the new paradigm will favor initiation at CD4 cell counts $\leq 350$ cells/µL, $\leq 500$ cells/µL, or even higher will await further developments.

WHAT TO START

The 2 most favored types of regimens for initiating therapy include 2 NRTIs plus either an NNRTI or a ritonavir-boosted protease inhibitor [1, 2]. Table 1 summarizes recent trials examining which NRTIs are best to combine with NNRTIs or boosted PIs and whether NNRTI- or PI-based therapy offers superior outcomes [30–38].

AIDS Clinical Trials Group (ACTG) Study 384, a randomized controlled trial, established EFV plus zidovudine (ZDV) plus 3TC as the best of 6 regimens evaluated [39, 40]. Starting treatment with this combination yielded the shortest time to viral suppression, delayed first virologic failure, and delayed failure of the first regimen. Four-drug regimens that were evaluated (i.e., d4T plus didanosine or ZDV plus 3TC, added to EFV plus nelfinavir) did not improve these outcomes [40]. A later trial found that the addition of abacavir (ABC) to EFV, ZDV, and 3TC also did not benefit treatment with EFV, ZDV, and 3TC in terms of time to virologic failure, proportion of subjects with a VL <50 copies/mL at 3 years, or increases in CD4 cell count [31].

Gilead Study 934 demonstrated that a combination of emtricitabine (FTC) plus TDF was superior to fixed-dose ZDV/3TC when either was added to EFV [32, 41]. A higher proportion of subjects receiving FTC/TDF reached and maintained a VL <50 copies/mL at 48 weeks (table 1) [32]. The differences remained significant at 96 and 144 weeks for a VL <400 copies/mL, although not for a VL <50 copies/mL [33, 41]. Subjects receiving FTC/TDF also showed larger increases in CD4 cell counts at 48 weeks (190 cells/µL vs. 158 cells/µL, respectively [95% CI for difference, 9–55 cells/µL]; $P = .002$). Again, this significant difference remained at 144 weeks (312 cells/µL vs. 271 cells/µL, respectively) [41]. Safety parameters also favored FTC/TDF. Subjects assigned to receive this regimen had significantly more limb fat at weeks 48 and 144, as measured by dual-energy x-ray absorptiometry (DEXA) scanning, in a met-
abolic sub study [29, 41]. Adverse events that resulted in treatment discontinuations also were more common among subjects receiving ZDV/3TC, compared with those receiving FTC/TDF (9% vs. 4%, respectively; \( P = .02 \)).

A prospective, randomized, phase 3 ACTG study has shed light on the benefits and disadvantages of EFV and LPV/r as the bases for initial therapy [34]. Subjects received EFV plus 2 NRTIs, LPV/r plus 2 NRTIs, or LPV/r plus EFV. EFV-based regimens demonstrated superior virologic efficacy, although LPV/r-based regimens yielded greater increases in CD4 cell counts. At week 96, the proportions of patients who had not experienced virologic failure were 75% with EFV plus 2 NRTIs, 73% with EFV plus LPV/r, and 67% with LPV/r plus 2 NRTIs (\( P = .006 \) for LPV/r- vs. EFV-containing regimens). In addition, a higher proportion of subjects receiving EFV-containing regimens achieved HIV RNA levels <50 copies/mL (table 1). Median increases in CD4 cell counts were greater with LPV/r-containing regimens: 268 cells/µL with LPV/r plus EFV and 285 cells/µL with LPV/r plus 2 NRTIs, compared with 239.5 cells/µL with EFV plus 2 NRTIs (\( P = .01 \)).

Time to treatment-limiting toxicity was similar for all regimens [34]. The NRTI-sparing regimen LPV/r plus EFV increased lipid levels more than either of the other 2 regimens but was associated with the lowest frequency of lipoatrophy, as measured by DEXA scanning as a \( >20\% \) loss of extremity fat (8% loss [LPV/r plus EFV], compared with 18% [LPV/r plus 2 NRTIs] or 32% [EFV plus 2 NRTIs]). LPV/r was associated with less lipoatrophy than was EFV when each was combined with 2 NRTIs. The frequency of lipoatrophy also varied with the NRTI used; only 10% of subjects receiving TDF-containing regimens developed this adverse effect, compared with 27% of those receiving ZDV and 43% of those receiving d4T [42].

Several PI-based regimens are appropriate for treatment-naive patients. These include 2 NRTIs plus either LPV/r, atazanavir/ritonavir, FPV/ritonavir (FPV/r), saquinavir/ritonavir, or possibly darunavir/ritonavir. Clinical trial data have demonstrated the utility of these ritonavir-boosted PI regimens in various patient populations, as shown in table 1 [30, 35–38].

One issue to consider when deciding on the nucleoside pair with which to initiate therapy is the hypersensitivity reaction associated with ABC that occurs in 5%–8% of white patients [43]. A major risk factor for ABC hypersensitivity is \( HLA-B^*5701 \). Two recent studies have demonstrated that prospective screening for \( HLA-B^*5701 \) can substantially reduce the frequency of ABC-associated hypersensitivity reactions, suggesting that such genetic screening should always precede the use of this agent [44, 45].

### Table 1. Representative recent clinical trials addressing initial combination antiretroviral therapy (ART) regimens (in chronological order).

<table>
<thead>
<tr>
<th>Study, follow-up period</th>
<th>No. of subjects</th>
<th>Regimens</th>
<th>Proportions of subjects with VL &lt;50 copies/mL, %</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG A5095 [31], 3 years</td>
<td>765</td>
<td>EFV + ZDV/3TC vs. EFV + ZDV/3TC/ABC</td>
<td>85 vs. 88</td>
<td>.39</td>
</tr>
<tr>
<td>Gilead Study 934 [32, 33]</td>
<td></td>
<td>EFV + FTC/TDF vs. EFV + ZDV/3TC</td>
<td>80 vs. 70</td>
<td>.02</td>
</tr>
<tr>
<td>ACTG 5142 [34], 96 weeks</td>
<td>753</td>
<td>EFV + 2 NRTIs vs. LPV/r + 2 NRTIs vs. EFV + LPV/r</td>
<td>89 vs. 77 vs. 83</td>
<td>.003</td>
</tr>
<tr>
<td>KLEAN [35], 48 weeks</td>
<td>878</td>
<td>ABC/3TC + FPV/r vs. ABC/3TC + LPV/r</td>
<td>66 vs. 65</td>
<td>...</td>
</tr>
<tr>
<td>089 Study Group [36], 48 weeks</td>
<td>200</td>
<td>3TC + d4T + ATV300/ritonavir vs. 3TC + d4T + ATV400</td>
<td>75 vs. 70</td>
<td>...</td>
</tr>
<tr>
<td>ARTEMIS [37], 48 weeks</td>
<td>689</td>
<td>TDF + FTC + DRV/r vs. TDF + FTC + LPV/r</td>
<td>84 vs. 78</td>
<td>...</td>
</tr>
<tr>
<td>Gemini [38], 48 weeks</td>
<td>337</td>
<td>TDF + FTC + SQV/r vs. TDF + FTC + LPV/r</td>
<td>64.7 vs. 63.5</td>
<td>...</td>
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**NOTE.**

3TC, lamivudine; ABC, abacavir; ACTG, AIDS Clinical Trials Group; ARTEMIS, Antiretroviral Therapy with TMC114 Examined in Naive Subjects; ATV, atazanavir; d4T, stavudine; DRV/r, darunavir/ritonavir; EFV, efavirenz; FPV/r, fosamprenavir/ritonavir; FTC, emtricitabine; KLEAN, Kaletra vs. Lexiva with Epivir and Abacavir in ART-Naive patients; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NRTI, nucleoside reverse-transcriptase inhibitor; SQV/r, saquinavir/ritonavir; TDF, tenofovir disoproxil fumarate; VL, viral load; ZDV, zidovudine.

- For the difference between proportions of subjects, 95% confidence intervals were 2%–17% at 48 weeks and 0.08%–17% at 144 weeks.
- For LPV/r vs. EFV-containing regimens.
- Noninferiority was demonstrated.
- An extended-release form of d4T that is not commercially available was used in both regimens.
- Nonsignificant for superiority in overall population (\( P < .062 \)) but significant for superiority in a subset of subjects with VL >100,000 copies/mL (79% [DRV/r] vs. 67% [LPV/r]; \( P < .05 \)).
of TDF/FTC/EFV is a widely used option. However, the EFV component cannot be prescribed early during pregnancy or for women contemplating pregnancy, and the TDF component poses risks for persons with preexisting renal failure. Nevirapine may be substituted for EFV for women who are in their first trimester of pregnancy or who have a high potential for pregnancy, if their CD4 cell count is <250 cells/µL. Combinations of 2 NRTIs or nucleotide RTIs and a ritonavir-boosted PI (i.e., lopinavir, atazanavir, FPV, or saquinavir) also are acceptable options for initial therapy.

Potential adherence and drug resistance also should be considered when making decisions about initial regimens. Multiple mutations often are required for high-level resistance to PIs, whereas single mutations often lead to NNRTI resistance. Moreover, ~7% of initial HIV infections in the United States are with NNRTI-resistant viruses, which is a substantially higher percentage than that for PI-resistant viruses (2.4%) [46]. Thus, if testing suggests primary (transmitted) NNRTI resistance, EFV should not be included in the initial regimen.

Each situation should be individualized, with the appropriate regimen chosen after careful discussion of all advantages and disadvantages between the health care professional and the patient. Adding agents does not necessarily improve outcome, and there is no good evidence that 4-drug regimens offer more benefits, compared with 3-drug regimens, for most individuals. Current or planned trials will further refine the preferable options for initial therapy (e.g., see [47]).

**New ARVs Recently Approved or in Late-Stage Development**

Several experimental or newly approved ARVs represent drugs in new classes of therapeutic agents that are active at novel sites in the HIV replicative cycle. These agents are currently being used primarily for individuals with limited or no options relative to the purposes of this discussion, only trials with treatment-naive subjects will be described.

A phase 2 trial of raltegravir monotherapy was conducted with 35 treatment-naive HIV-1–infected subjects [49]. Several doses between 100 and 600 mg twice daily for 10 days were evaluated versus placebo. Substantial antiviral activity was observed at all doses of raltegravir, and no serious adverse events were described.

This trial was expanded into a phase 2 comparison of different doses of raltegravir and EFV, both in combination with TDF and 3TC [50]. At a planned 24-week analysis, similar proportions of patients had achieved HIV RNA levels <50 copies/mL with 4 doses of raltegravir or with EFV combined with 3TC and TDF (N = 197). VL fell more quickly in all groups receiving raltegravir than in the group receiving EFV, but the reductions were equivalent to those in the EFV group by 24 weeks. The clinical significance of this observation is uncertain. Increases in CD4 cell count were comparable across arms. In general, adverse effects were mild and comparable, except that headache, dizziness, and abnormal dreams occurred more frequently in the EFV group. Raltegravir had little effect on serum cholesterol and triglyceride levels, whereas slight increases were seen in the EFV group [51]. Durable antiviral activity was observed during a subsequent 48-week analysis of study results [52]. Other integrase inhibitors, such as elvitegravir, are being studied, but data for treatment-naive patients have not yet been presented.

**CCR5 antagonists.** HIV attachment and entry are complex multistep processes involving initial attachment, coreceptor binding, and membrane fusion. CCR5 antagonists interfere with an aspect of HIV entry into CD4 cells that relies on the use of the chemokine receptor CCR5. HIV-1 can enter cells by using CCR5, CXC4, or both receptors. CCR5 inhibitors act only on viruses that use the CCR5 receptor (R5 viruses). One CCR5 antagonist, maraviroc, was FDA approved in 2007 for use with treatment-experienced patients. Another CCR5 antagonist, vicriviroc, is in an advanced stage of development. In trials with highly treatment-experienced patients, both maraviroc and vicriviroc have demonstrated considerable activity [53–55]. These agents also are being studied in patients with earlier-stage infection, including those who are treatment naive. Since most patients have predominantly R5 viruses early during infection, these agents may be particularly useful in such situations. In a randomized, double-blind trial comparing maraviroc with EFV, both in combination with ZDV/3TC, in treatment-naive subjects (the MERIT study), results at 48 weeks suggested that maraviroc did not demonstrate noninferiority for the end point of HIV RNA level <50 copies/mL, when compared with EFV [56]. However, studies with treatment-naive subjects are still under way, and no conclusions can be drawn concerning these agents as part of initial therapeutic regimens.

**New NNRTIs.** Although several NNRTIs are under investigation, only 1 is currently being studied in phase 3 trials with treatment-naive subjects. Riplivirine (TMC278), a diarylpyrimidine derivative, has anti-HIV activity in nanomolar con-
centrations [57]. Because the results of pilot studies with treat-
ment-naive subjects looked promising [58], a larger, phase 2, 
dose-finding study of rilpivirine was conducted with 368 treat-
ment-naive subjects [59]. Subjects were randomized to receive 
either open-label EFV or 1 of 3 blinded doses of rilpivirine. 
Virologic responses were similar for all 4 of the study arms, as 
were changes in CD4 cell count; 77%–81% of subjects in all 
groups reached VLs <50 copies/mL at 48 weeks. Adverse-event 
profiles were similar among the groups, although central nerv-
ous system symptoms and rash were more common in the 
EFV group. Rilpivirine is being developed further for treat-
ment-naive patients and is being compared with EFV in large 
phase 3 trials.

CONCLUSIONS

Over the past 2 decades, the progress made in HIV therapy has 
been enormous, with one study suggesting that ∼3 million years 
of life have been saved since 1989 because of antiretroviral drugs 
[60]. With improvements in drugs and regimens and through 
the conduct of carefully controlled clinical trials, durable HIV 
suppression should occur in the majority of treated individuals. 
An analysis of published trial results has suggested that the 
proportion of patients attaining VLs <50 copies/mL at 48 weeks 
has risen from 41% before 1998 to 64% in 2003–2004 [61]. 
More-recent data suggest that the current response rate should 
be ≥80% [32, 34].

Decisions regarding when to begin therapy have implications 
for the individual patient as well as for public health. There 
are no conclusive data regarding whether to treat individuals 
with primary acute HIV infection, but initiation of such therapy 
is a reasonable choice. To retain the potential benefits of such 
early treatment, however, cART started at that stage should not 
be discontinued except in the context of a clinical trial.

The optimal time to begin cART for chronically infected 
individuals has not been established, although current guide-
lines suggest that beginning treatment when CD4 cell counts 
are between 200 and 350 cells/µL is appropriate. As regimens 
increase in both potency and tolerability, good arguments can 
be made for beginning therapy even earlier. Several regimens 
can be considered for initial therapy, and choices should be 
individualized, depending on patient-specific factors. It is likely 
that therapeutic choices will continue to expand as new drugs 
and new regimens become available. Carefully controlled clin-
cial trials will continue to be the driving force in determining 
the optimal regimens for patient care.

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