Managing Antiretroviral Therapy: Changing Regimens, Resistance Testing, and the Risks from Structured Treatment Interruptions

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The management of patients receiving therapy for human immunodeficiency virus infection has improved in recent years owing to factors such as new classes of antiretroviral drugs, new agents in existing classes, and reduced resistance rates when chronically infected patients begin treatment with preferred regimens. Transmitted resistance variants in ∼10% of treatment-naive patients underline the need for pretreatment resistance testing, to improve rates of virologic efficacy. Structured treatment interruptions to reduce drug exposure and toxicity should not be used outside well-controlled research studies, since this practice has been associated with increased rates of death and disease progression.

Major issues in managing HIV-infected patients receiving antiretroviral therapy (ART) include when to switch ART regimens because of a lack of virologic efficacy, what combination of medications to switch to, application of resistance testing, and whether structured treatment interruptions are ever an appropriate management strategy. In particular, structured treatment interruptions in which treatment is stopped at a CD4 cell count of 350 cells/µL and resumed at 250 cells/µL have been associated with increased morbidity and mortality [1, 2].

WHEN TO SWITCH ART BECAUSE OF VIROLOGIC FAILURE

Whether to switch ART because of insufficient virologic suppression is a complex decision that is not triggered solely by a given viral load (VL) or CD4 cell count threshold. Considerations include the patient’s virologic, immunologic, and clinical status; his or her history of toxicity to or tolerance of antiretroviral agents (ARVs); results of resistance testing; and the availability of ≥2 active ARVs from which to construct a new regimen.

Is the patient experiencing virologic failure? The goal even for highly treatment-experienced patients is a VL below the limit of detection. Virologic failure, therefore, is defined as confirmed, measurable VL in the presence of treatment, as follows [3]: ≥400 copies/mL at ≥24 weeks, ≥50 copies/mL at ≥48 weeks, and repeated VLS ≥400 copies/mL after prior suppression to <400 copies/mL. These definitions provide important end points for clinical trials, but virologic failure does not always equal immunologic or clinical failure. Results from clinical trials that address the management of individuals with low-level viremia (VL, 50–1000 copies/mL) are unavailable, and resistance testing may not be successful if plasma HIV RNA level is <1000 copies/mL. Therefore, HIV health care providers must rely on clinical judgment, expert opinion, patient input, and analysis of the individual patient’s clinical situation when deciding how to respond to so-called virologic failure. An initial step is to try to determine the causes of viral replication during therapy.

If there is virologic failure, then why? Determining
the reason(s) for virologic failure is important to ascertaining the best course of action. Potential causes include insufficient ARV levels, inadequate potency of individual ARVs or a combination of ARVs, and preexisting resistance. Insufficient drug levels may stem from suboptimal adherence (owing to toxicity, tolerability, or personal issues), poor absorption, host genetics that influence drug metabolism, incorrect dose, or drug interactions.

**If a switch is needed, then when?** When to switch ART in the presence of virologic failure is not clearly defined. Most guidelines suggest switching ART when there are ≥2 fully active ARVs from different classes available from which to construct a new regimen [3, 4]. The use of ≥2 fully active ARVs increases the probability of success [5]. Determining whether ≥2 active ARVs from different classes are available requires resistance testing to detect current mutations, as well as analysis of the results of past resistance tests and prior ARV exposure, and assessment of the patient’s history regarding treatment toxicity and ability to tolerate previous ART.

If a regimen that includes ≥2 active ARVs cannot be constructed, then consideration should be given to whether the patient’s clinical status allows the option of waiting until new ARVs are available from which to build an appropriate regimen. Factors that strongly favor switching promptly even without ≥2 active ARVs include rapidly declining or low CD4 cell counts (<100 cells/µL), low CD4 cell count nadir, the return of HIV/AIDS signs and symptoms, and active AIDS-defining illnesses [3, 6]. For patients without these characteristics, consideration should be given to delaying a switch until either new ARVs are approved or clinical status deteriorates. Knowing when new ARVs are likely to become available through expanded access or US Food and Drug Administration (FDA) approval is an important factor in the timing of an ART regimen switch for some patients.

Findings from the T-20 versus Optimized Regimen Only studies of enfuvirtide (ENF) suggest which triple-drug-class–experienced patients are likely to succeed with a new regimen. Factors associated with achieving a VL of <400 copies/mL at 48 weeks were a baseline CD4 cell count >100 cells/µL, a baseline HIV RNA level <100,000 copies/mL, and prior use of ≤10 ARVs, as well as ≥2 active ARVs in the optimized background regimen (OBR) [5].

**What if the decision is not to switch?** Risks resulting from not switching appear to be lower than might be expected. Some data suggest that patients with more mutations acquire additional major resistance relatively slowly. In 1 cohort, ~30% of patients (N = 106) who were receiving maintenance therapy with a partially suppressive regimen (VL, ≥500 copies/mL) lost the phenotypic equivalent of 1 drug to which HIV is susceptible, at 1 year (median follow-up, 11.3 months) [7]. Fewer mutations at baseline significantly predicted the risk of developing new nucleoside reverse-transcriptase inhibitor (NRTI) resistance mutations (P = .01) [7]. My colleagues and I reported similar findings [8], with an incidence rate of 1.61 acquired mutations/person-year (95% confidence interval [CI], 1.36–1.90 acquired mutations/person-year; N = 98). It may be acceptable to await soon-to-be-available ARVs, especially those that are likely to have full antiretroviral activity, rather than switching treatment for clinically stable patients who currently do not have ≥2 active ARVs with which to construct a new regimen.

For patients who continue to receive a failing regimen, the goal shifts toward preservation of clinical and immunologic stability [3]. Continuing ART is crucial because it is associated with benefits even in the presence of viral replication. Treatment that maintains VL at <10,000 copies/mL has been linked to an upward slope in CD4 cell count [6]. Treatment interruption has been associated with serious risks and is not recommended (see Risks from Structured Treatment Interruptions) [1, 9, 10]. Continuing therapy with an NRTI even for patients with multidrug-resistant (MDR) HIV infection is important, since stopping these ARVs has been associated with an immediate increase in VL [11]. Many clinicians also would maintain ritonavir-boosted protease inhibitor (PI) therapy but would avoid nonnucleoside reverse-transcriptase inhibitor (NNRTI) therapy, owing to the risk of evolution of additional NNRTI resistance mutations that may compromise second-generation NNRTI therapy.

**WHAT TO SWITCH TO**

Developing a new regimen requires resistance testing and evaluation of the patient’s history of treatment, adherence, and toxicity. Resistance testing is more effective at predicting a poor response than a good response. Concomitant conditions such as liver disease, renal failure, or anemia may influence the choice of ARVs. Patients with active hepatitis B virus infection should continue to receive ARVs that are effective against this virus; these include lamivudine (3TC), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF) or a specific hepatitis B virus antiviral such as entecavir, adefovir, or telbivudine. Recently, entecavir has been shown to have modest antiretroviral activity and to select for the M184V mutation. It, therefore, should not be used to treat hepatitis B virus infection in the absence of specific anti-HIV therapy [12]. Previous ARV-related toxicity (e.g., peripheral neuropathy, pancreatitis, and hypersensitivity) may limit treatment choices.

**New Drug Class**

An ARV from a new drug class is likely to have potent activity and to not be limited by cross-resistance. Studies of ENF, which until 2007 represented the only new class of anti-HIV ARVs approved since 1996, demonstrated significantly superior virologic suppression, compared with OBRs containing 2–4 active
ARVs [13]. Adding ENF to a new ARV in an existing class (e.g., tipranavir/ritonavir [TPV/r] or darunavir/ritonavir [DRV/r]) also improved virologic response (figure 1) [14, 15].

ENF. ENF is the only available HIV-1 fusion inhibitor. Early virologic response (at least 1-log reduction at 12 weeks) predicts durable response (VL <50 copies/mL, achieved in 39.2% of patients [95% CI, 33.6%–44.8%], or <400 copies/mL, achieved in 59.5% of patients [95% CI, 53.8%–65.1%], at 96 weeks) [16]. Pneumonia and lymphadenopathy occurred significantly more often among ENF-treated patients than among control subjects (6.7 vs. 0.6 cases/100 patient-years with ENF vs. OBR, respectively), although the incidence of pneumonia was within the expected range for the population [17].

Raltegravir (MK-0518). Raltegravir is the first HIV-1 integrase inhibitor approved for marketing by the FDA. It blocks integrase, a viral enzyme required for the integration of HIV into host cellular DNA [18]. When added to an OBR, raltegravir has demonstrated impressive preliminary efficacy and safety in 2 randomized, placebo-controlled, phase 3 trials with triple-drug-class–resistant patients (combined N = 699) [19, 20]. In this hard-to-treat population, the proportion of patients attaining a VL of <400 copies/mL at 16 weeks significantly favored raltegravir over placebo (77% vs. 41%–43%; P <.001). The adverse-event profile for raltegravir was similar to that for placebo. A 24-week, phase 2b, dose-ranging trial (N = 178) reported similar results [21]: regardless of the dose used (200, 400, or 600 mg twice/day), significantly higher proportions of patients achieved a VL of <400 copies/mL and <50 copies/mL with raltegravir plus an OBR (P <.0001 for all comparisons with placebo plus OBR). Raltegravir has demonstrated additive or synergistic activity in vitro with all approved anti-HIV ARVs with which it has been tested. Concomitant use of atazanavir
increases raltegravir levels, although the increase is not believed to be clinically significant [22].

**Maraviroc.** Maraviroc is a CCR5 antagonist that blocks the use of this coreceptor by HIV-1 and its subsequent entry into the cell. Maraviroc is the first drug in this class to be approved by the FDA and the European Medicines Agency for use with treatment-experienced patients. HIV-1 variants use either CCR5 (R5 viruses), CXCR4 (X4 viruses), or both (dual-tropic variants). The most commonly used method for determining viral tropism of viruses from infected individuals does not distinguish between mixtures of R5 and X4 variants and those that are truly dual tropic. Therefore, the designation “dual/mixed-tropic virus” has been used. In patients infected with dual/mixed-tropic or CXCR4-tropic virus, the antiretroviral efficacy of maraviroc was not better than that of placebo [23]. However, maraviroc has demonstrated significant efficacy in patients with CCR5-tropic virus. Roughly double the proportion of triple-drug-class–experienced patients (with CCR5-tropic virus only) achieved a VL of <400 copies/mL at 24 weeks with maraviroc given twice/day, compared with those given placebo, when each regimen was combined with an OBR, according to interim findings of 2 randomized, phase 2b/3 trials (60.4% vs. 31.4% and 61.3% vs. 23.1%, respectively; \( P < .0001 \) for both comparisons; combined \( N = 1049 \) [24, 25]. The differential was similar for a VL of <50 copies/mL at 24 weeks in the 2 trials (48.5% vs. 24.6% [\( P < .0001 \)] and 40.8% vs. 20.9% [\( P = .0005 \)], respectively) [24, 25]. Antiviral activity has been shown to persist at a similar level through 48 weeks of therapy [26].

### New ARVs in Existing Classes

New ARVs in existing classes may have substantial activity, although resistance to previously selected ARVs in the same class may reduce efficacy. Two new PIs, TPV/r and DRV/r (TMC114/r), were approved in the past 2 years. Genotyping (for TPV/r) or phenotype and genotype analysis (for DRV/r) predicts susceptibility to these ARVs in highly treatment-experienced patients [27, 28]. Resistance testing provides critical information when choosing whether to use 1 of these ARVs or another. An NNRTI, etravirine (TMC125), also was recently approved by the FDA. This ARV has activity against HIV variants with resistance to first-generation NNRTIs [29].

#### PIs

Table 1 summarizes the 48-week virologic suppression achieved with TPV/r and DRV/r in their major clinical trials [14, 15, 19, 20, 24, 25, 30, 31]. Both offer excellent efficacy. DRV/r appears to have a better safety profile, although no head-to-head comparisons of these 2 PIs have been completed. Patients receiving TPV/r must be monitored frequently for elevations in liver-enzyme levels and increased cholesterol or triglyceride levels, since these adverse effects occurred more often than in patients receiving a comparator PI/ritonavir (CPI/r) regimen during clinical trials [32]. In phase 3 trials, ~6% of patients who received TPV/r developed grade 3–4 elevations in transaminase levels [32]. Increases in triglyceride levels were roughly twice as common with TPV/r than with a CPI/r regimen (21.7%–20% vs. 10.2%–12.5%, respectively, at 24 weeks) [33, 34]. Fatal and nonfatal intracranial hemorrhage has been reported with TPV/r [32]. In contrast, the adverse-event profile of DRV/r (data at 24 weeks) was similar to that of CPI/r regimens [15, 35].

<p>| Table 1. Proportion of patients reaching a viral load (VL) of &lt;50 copies/mL with use of antiretroviral therapy (ART) with the newest antiretroviral agents. |</p>
<table>
<thead>
<tr>
<th>Study [reference], treatment regimen</th>
<th>Patients with VL &lt;50 copies/mL, %a</th>
<th>( P )</th>
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<tbody>
<tr>
<td><strong>RESIST-1 and -2 at 48 weeks [14]</strong></td>
<td></td>
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<tr>
<td>TPV/r: 500 mg/200 mg b.i.d.</td>
<td>22.8 (170/749)</td>
<td>( &lt;.0001 )</td>
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<tr>
<td>CPI/r</td>
<td>10.2 (75/737)</td>
<td></td>
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<tr>
<td><strong>POWER 1 and 2 at 48 weeks [15]</strong></td>
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<tr>
<td>DRV/r: 600 mg/100 mg b.i.d.</td>
<td>45 (50/110)</td>
<td>( &lt;.0001 )</td>
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<tr>
<td>CPI/r</td>
<td>10 (12/120)</td>
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<tr>
<td><strong>BENCHMRK-1 at 16 weeks [19]</strong></td>
<td></td>
<td></td>
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<tr>
<td>Raltegravir: 400 mg b.i.d.</td>
<td>61 (232)</td>
<td>( &lt;.001 )</td>
</tr>
<tr>
<td>Placebo</td>
<td>33 (118)</td>
<td></td>
</tr>
<tr>
<td><strong>BENCHMRK-2 at 16 weeks [20]</strong></td>
<td></td>
<td></td>
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<tr>
<td>Raltegravir: 400 mg b.i.d.</td>
<td>62 (230)</td>
<td>( &lt;.001 )</td>
</tr>
<tr>
<td>Placebo</td>
<td>36 (119)</td>
<td></td>
</tr>
<tr>
<td><strong>MOTIVATE 1 at 24 weeks [24]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>48.5 (235)</td>
<td>( &lt;.0001^b )</td>
</tr>
<tr>
<td>150 or 300 mg b.i.d.</td>
<td></td>
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<tr>
<td>150 or 300 mg q.d.</td>
<td>42.2 (232)</td>
<td>( .0006^b )</td>
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<tr>
<td>Placebo</td>
<td>24.6 (118)</td>
<td></td>
</tr>
<tr>
<td><strong>MOTIVATE 2 at 24 weeks [25]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>40.8 (191)</td>
<td>( .0006^b )</td>
</tr>
<tr>
<td>150 or 300 mg b.i.d.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 or 300 mg q.d.</td>
<td>45.6 (182)</td>
<td>( &lt;.0001^b )</td>
</tr>
<tr>
<td>Placebo</td>
<td>20.9 (91)</td>
<td></td>
</tr>
<tr>
<td><strong>DUET-1 at 24 weeks [30]</strong></td>
<td></td>
<td></td>
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<tr>
<td>Etravirine: 200 mg b.i.d.</td>
<td>56 (170/304)</td>
<td>.005</td>
</tr>
<tr>
<td>Placebo</td>
<td>39 (119/308)</td>
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</tr>
<tr>
<td><strong>DUET-2 at 24 weeks [31]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etravirine: 200 mg b.i.d.</td>
<td>62 (183/295)</td>
<td>.0003</td>
</tr>
<tr>
<td>Placebo</td>
<td>44 (129/296)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** b.i.d., twice/day; CPI/r, ritonavir-boosted comparator protease inhibitor; DRV/r, darunavir/ritonavir; MOTIVATE, Maraviroc plus Optimized Background Therapy in Viremic, ART-Experienced Patients; POWER, Performance of TMC114/r When Evaluated in Treatment-Experienced Patients with Protease-Inhibitor Resistance; q.d., every day; RESIST, Randomized Evaluation of Strategic Intervention in multidrug-resistant patients with Tipranavir; TPV/r, tipranavir/ritonavir.

a Data in parentheses are no. of patients/total no. of patients receiving regimen or total no. of patients receiving regimen.

b Compared with placebo.
Patients receiving DRV/r who had ≥1 active ARV in an OBR demonstrated a better response, with 53.6% achieving a VL of <50 copies/mL at 48 weeks. This again illustrates the importance of including ≥2 active ARVs in a new regimen for treatment-experienced patients; presumably, DRV/r offered a second active ARV for these individuals [15].

**NNRTIs.** Findings from a relatively small study suggest that etravirine adds antiviral benefits in patients with highly resistant virus [29]. Preliminary data on reverse-transcriptase mutations that lead to a decreased response to etravirine are being generated [36]. Some of the mutations that have an impact on susceptibility are previously described resistance mutations to first-generation NNRTIs, although mutational patterns are complex and, typically, multiple mutations are present with a decreased response to etravirine-based therapy. Data on phenotypic resistance cutoffs should be forthcoming.

Findings from 2 large phase 3 studies (N = 612 and 591) indicate that etravirine adds antiretroviral activity in patients with highly resistant virus (e.g., ≥3 primary PI resistance mutations and documented resistance to NNRTI) [30, 31]. Etravirine added to DRV/r plus optimized NRTI therapy improved the proportion of patients who achieved a VL of <50 copies/mL at 24 weeks, from 17% to 18%. Tolerability to etravirine was similar to that for placebo, although more rashes occurred among the patients receiving etravirine [31]. Thirteen reverse-transcriptase mutations appear to be associated with a decreased response to etravirine. Treatment response to etravirine in the DUET studies did not decrease substantially until ≥3 of these mutations were present [36].

### Value of Maintaining NRTIs

Most clinicians include an NRTI in ART regimens for highly treatment-experienced patients, because these ARVs are likely to retain some activity, although some debate exists. Stopping NRTI therapy for patients with MDR HIV infection who were experiencing treatment failure led to an immediate VL increase in all 6 subjects in one study (figure 2) [11]. In contrast, VL remained stable when patients interrupted the PI component of therapy (n = 18).

3TC in particular maintains effectiveness even in the presence of the M184V mutation, appearing to account for an approximately half-log increase in viral suppression at 48 weeks. VL rose by a mean of 0.57 log10 copies/mL when 3TC therapy was maintained, compared with 1.11 log10 copies/mL when all ARVs were stopped ([P = .0015; N = 58]) [37]. Stopping zidovudine/3TC therapy also led to a rapid increase in VL (median increase of 0.54 log10 copies/mL vs. baseline within 2 weeks [n = 16]) [38]. The continued efficacy of 3TC likely results from residual antiviral activity, although reduced viral fitness of HIV-1 variants with the M184V mutation is also a possibility [39].

Switching NRTIs in regimens has led to little change in viral suppression, however [40]. Nucleosides and TDF in regimens for highly treatment-experienced patients contributed little to no additional antiretroviral activity in trials of ENF. Switching NRTI therapy for highly treatment-experienced patients most likely maintains NRTI activity or adds modest activity at best. The addition of at least 1 active NRTI in ENF trials conferred a decrease in VL of 0.18 log10 copies/mL, with the exception of zidovudine, which added a quarter-log reduction in HIV
RNA level [40]. Given that most patients were switching from one NRTI-containing regimen to another, whether residual NRTI activity contributed to the success of the ENF-containing regimen could not be assessed in these trials.

**UTILITY OF RESISTANCE TESTING**

Resistance testing is crucial to guiding treatment for HIV infection and should be done with cases of acute infection (e.g., <12 months); for chronically infected patients prior to therapy; during pregnancy, if the mother is viremic; and during virologic failure [3, 41, 42]. Testing of patients with chronic infection is intended to detect transmitted mutations that persist for prolonged periods [43]. Persistence of resistant virus in male genital secretions specifically has been documented [44]. Whether to test all chronically infected, treatment-naive patients or to reserve resistance testing for patients who are thought to have been infected more recently is a matter of debate. Modeling data suggest that even a low level of resistance in the untreated population makes resistance testing cost-effective [45], and current guidelines of the US Department of Health and Human Services (DHHS) recommend testing for all chronically infected, treatment-naive patients [3, 4].

**Spectrum of resistance.** Several major patterns of multi-NRTI resistance mutations have been identified. Thymidine-analogue–associated mutations are the most common. K65R, which is selected by abacavir and tenofovir and possibly by stavudine, leads to relatively broad cross-resistance, although viruses with K65R remain susceptible or may be hypersusceptible to zidovudine. In addition, there are 2 less-common mutational patterns that lead to broad cross-resistance: one is a complex of mutations that includes codon 151, called the “Q151M mutation complex,” and the second includes multiple amino acid insertions at codon 69. Both of these genotypic patterns lead to broad nucleoside cross-resistance, although viruses with Q151M cross-resistance may retain susceptibility to tenofovir. Fortunately, the Q151M mutation complex and the codon 69 insertion complex are less common. The 3TC/FTC resistance mutation M184V may be one of the most common in treatment-experienced patients, although this mutation leads to increased susceptibility to zidovudine and tenofovir.

Approximately 16 distinct NRTI resistance mutations are listed in the most recent update of the International AIDS Society–USA Drug Resistance Mutations Group [46]. Fewer (~11) NNRTI resistance mutations have been described, but most contribute to NNRTI cross-resistance. Three of these mutations are associated with etravirine. The protease enzyme is more malleable of the 2 proteins, with ~12 positions associated with major mutations and 31 more sites associated with minor mutations [46]. Consistent definitions of transmitted drug resistance are needed. A recent publication offers a standardized list of drug-resistant mutations that are suggestive of transmitted drug resistance [47].

**Transmission of resistance in ARV-naive patients.** Genotyping of HIV in chronically infected, ARV-naive patients is cost-effective if the resistance prevalence is >1% [43]. Both Europe and the United States substantially exceed that threshold (table 2) [48–50]. The presence of drug-resistant HIV strains has been associated with suboptimal virologic response to initial ART [3]. Baseline NNRTI resistance more than doubled the risk of virologic failure in response to initial NNRTI-containing ART in AIDS Clinical Trials Group A5095 (intent-to-treat hazard ratio [HR], 2.27 [95% CI, 1.15–4.49]; P = .018) [51]. Approximately one-third of patients who developed virologic failure during the FTC-301A trial had baseline resistance mutations, most commonly to NNRTIs [52].

**Is the prevalence of MDR HIV variants declining among chronically infected, treated patients?** The risk of acquiring triple-drug-class resistance appears to be low for those who begin therapy with combination ART (cART). In the University of North Carolina HIV Cohort study [53], the prevalence of triple-drug-class resistance was 3% (95% CI, 2%–4%) among those receiving cART as first-line therapy (n = 789), compared with 12% (95% CI, 10%–15%) among those initially treated with non-cART (n = 798). The number of prior ARVs, as well as exposure to non-cART, was independently associated with resistance development over a median follow-up time of 4 years [53]. These findings are consistent with those of an earlier analysis. At 6 years after the start of cART, the failure of triple-drug-class therapy had occurred in 11.2% of patients for whom cART was their first ART, compared with 21.4% of those who began anti-HIV treatment with non-cART (P < .0001; N = 3496) [54].

**Resistance testing during virologic failure.** Genotypic resistance testing of HIV in 326 patients experiencing virologic

<table>
<thead>
<tr>
<th>Type of resistance mutation</th>
<th>Prevalence in the United States, %</th>
<th>Prevalence in Europe, 2002–2003, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>6.4</td>
<td>3.6</td>
</tr>
<tr>
<td>NNRTI</td>
<td>1.7</td>
<td>6.9</td>
</tr>
<tr>
<td>PI</td>
<td>1.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Multiclass</td>
<td>1.3</td>
<td>1.4^d</td>
</tr>
<tr>
<td>Overall</td>
<td>8.3</td>
<td>10.4</td>
</tr>
</tbody>
</table>

**NOTE.** NRTI, nonnucleoside reverse-transcriptase inhibitor; NNRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

^a N = 1082 [48].

^b N = 3130 [49].

^c N = 1083 [50].

^d ≥2-drug-class resistance.

^e 2-drug-class resistance.
failure increased the probability of reaching a VL of <400 copies/mL at week 24 of ART for highly treatment-experienced patients, compared with expert advice alone (48.5% vs. 36.2%, respectively; P < .05) [55]. Phenotypic resistance testing also has improved virologic response by guiding the choice of therapy for highly treatment-experienced patients experiencing virologic failure [56]. Genotypic resistance testing is preferable to phenotypic resistance testing for treatment-naive patients [3]. The utility of phenotypic resistance testing may increase with treatment experience and mutational complexity.

Resistance testing of HIV in a patient experiencing virologic failure should be performed while the patient is still receiving therapy or within 4 weeks after treatment has been discontinued [3]. DHHS guidelines advise the deferral of testing when VL is <1000 copies/mL, because virus amplification is unreliable [3]. This differs from the International AIDS Society–USA Panel recommendation to test at a VL of >500–1000 copies/mL [4]. Results of resistance testing always need to be interpreted carefully. The absence of resistance does not guarantee antiviral activity. Resistance testing performed on samples with lower VLs (<1000 copies/mL) may be less likely to be successful (and therefore may increase cost), and the results may be somewhat less reliable at low copy numbers.

Resistance testing identifies only the most prominent mutations circulating at a single time point. Minority species that may reemerge rapidly during drug exposure may not be detected. A single test may underestimate the presence of drug resistance. The analysis of mutational profiles from 1734 treatment-experienced patients that were based on their most recent and historical genotypes revealed at least 1 major mutational difference in 53.4% of patients [57]. Nearly two-thirds of those in whom the most recent and historical genotypes were the same had no major resistance mutations in any genotypic study [57]. Most patients with resistance mutations displayed differences in their most recent and historical genotype profiles.

RISKS FROM STRUCTURED TREATMENT INTERRUPTIONS

Historically, structured treatment interruptions have been commonplace during HIV care. Recent evidence indicates that the routine use of this strategy should be avoided. Compared with continuous treatment, CD4 cell count–guided interruption of therapy significantly increased the risk of death and disease progression in 2 studies, one in developed countries and the other in a developing-world setting [1, 2].

Reasons that have been advanced for the use of structured treatment interruptions have included conserving resources, limiting toxicity, and avoiding treatment fatigue. A large study (N = 5472) examined some of these rationales by randomization of patients to receive continuous therapy or to have therapy interrupted when their CD4 cell count reached 350 cells/µL, followed by resumption of therapy at a CD4 cell count of 250 cells/µL [1]. Accrual for this study, known as the Strategies for Management of Antiretroviral Therapy (SMART) study, was stopped after 16 months (mean) of follow-up, owing to safety concerns. The risk of opportunistic disease or death from any cause (the primary end point) was more than twice as common in the structured treatment interruption group (HR, 2.6 [95% CI, 1.9–3.7]; P < .001) [1]. Structured treatment interruptions were associated with a significantly increased risk of major cardiovascular, renal, or hepatic disease (HR, 1.7 [95% CI, 1.1–2.5]; P = .009). Only 8% of deaths resulted from opportunistic disease; the most common causes were nonopportunistic cancers and cardiovascular disease [1].

Differences in most-recent CD4 cell count and VL explained much, although not all, of the difference in risk. The risk of death from causes other than opportunistic disease was significantly higher in the structured treatment interruption group before adjustment for most-recent VL and CD4 cell count. The risk of fatal or nonfatal opportunistic disease remained significantly higher in the structured treatment interruption group even after this adjustment (adjusted HR 1.7 [95% CI, 1.0–2.9]) (figure 3) [1]. Even among patients with higher CD4 cell counts (>350–499 cells/µL and ≥500 cells/µL), however, significantly more instances of death or opportunistic disease occurred among those assigned to the structured treatment interruption group [58]. This association of death and opportunistic infection with not receiving therapy even at CD4 cell counts ≥350

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Figure 3. Estimated unadjusted and adjusted hazard ratios (drug-conservation group [n = 2720] vs. viral-suppression group [n = 2752]) for opportunistic disease or death from any cause, opportunistic disease (fatal or nonfatal), and death from causes other than opportunistic disease in the Strategies for Management of Antiretroviral Therapy (SMART) study. Bars indicate 95% confidence intervals. Adapted from [1], with permission from the Massachusetts Medical Society.
cells/µL or ≥500 cells/µL raises the question of whether discontinuing therapy poses risks.

The risk of some non–HIV-related events (e.g., cardiovascular disease outcomes) may have been increased by the impact of therapy cessation on inflammatory markers. Phillips et al. [59] have suggested that discontinuing ART may negatively affect lipids by contributing to a reduction in levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and total cholesterol (TC), leading to a net unfavorable change in the TC/HDL-C ratio.

A similar but smaller randomized study (N = 326; median follow-up time, 20 months) in the developing world that used the same CD4 cell count thresholds as used in the SMART study reported substantially similar conclusions [2]. The incidence of severe morbidity (i.e., World Health Organization stage 3 or 4 morbidity and any morbidity leading to death) was significantly higher in the structured treatment interruption group (P < .001), although the incidence of death was similar between the groups [2]. Most clinical events were cases of bacterial infection or tuberculosis.

The Staccato study obtained somewhat contrasting results by using a higher threshold for resuming therapy [60]. Patients were randomized to a structured treatment interruption group at CD4 cell counts >350 cells/µL, and treatment was resumed at CD4 cell counts <350 cells/µL. Similar proportions of patients reached a VL of <50 copies/mL, the primary end point (90.5% in the structured treatment interruption group and 91.8% in the continuous-therapy group). No AIDS-defining events occurred. Low CD4 cell counts and what the authors referred to as “minor manifestations of HIV infection” occurred more frequently in the structured treatment interruption group. The median time undergoing treatment was 21.9 months.

Differences in design and population may explain some of the divergence between these findings and those of the SMART study. By design, patients in the Staccato study were maintained at higher CD4 cell counts than those in the SMART study, since therapy was resumed at 350 cells/µL versus 250 cells/µL, respectively. In addition, small but significant distinctions between continuous and interrupted therapy may have been missed in the Staccato study owing to its smaller size (N = 430).

Patients in a clinical practice stop ART for a variety of reasons, many of which are unavoidable (e.g., recovery from toxicity) or are deemed in the patient’s best interest after an informed discussion between the patient and the clinician. The routine use of treatment interruptions or treatment “holidays” should be avoided. Patients who need to interrupt therapy for reasons of toxicity, adherence, or treatment fatique should be monitored very carefully when therapy is stopped.

When therapy that includes an NNRTI and an NRTI is interrupted, discontinuing the medications simultaneously may lead to prolonged NNRTI exposure because of the longer NNRTI half-life. This prolonged exposure to “monotherapy” may select for resistance. Although no precise strategy has been defined, many clinicians will stop the NNRTI component ~1 week prior to stopping the NRTI component of the therapy. Alternatively, some clinicians will switch the patient briefly to a PI-containing regimen and then discontinue therapy. These strategies may reduce the risk of NNRTI resistance.

Resensitization of resistant virus. Other studies have evaluated whether structured treatment interruption facilitates the reemergence of drug-susceptible virus, in the hope of enhancing virologic response. This strategy not only did not reduce VL but also led to significantly lower CD4 cell counts and a transiently elevated risk of death or disease progression (N = 254) [10, 61]. The risk of these outcomes was elevated during the 7.6 months immediately following the structured treatment interruption (HR 2.57 [95% CI, 1.2–5.5]; P = .01) [9].

Treatment interruption for the reversal of resistance mutations yielded only temporary benefit. After a structured treatment interruption (median duration, 24 weeks), HIV was susceptible to ≥3 drugs in 70% of patients (16 of 23) in an open-label study. However, all baseline resistance mutations recurred after treatment interruption, and 65% of patients (15 of 23) experienced an AIDS-defining event [62]. In another study, only 28% of patients (N = 39) experienced extensive reversion to wild-type virus during treatment interruption. The authors concluded that the persistence of resistant virus explained the lack of improved virologic suppression with structured treatment interruptions [61].

Stimulation of HIV-1–specific immune responses. Another rationale for the interruption of ART is to improve host immune control. Rosenberg et al. [63] stopped therapy for 8 patients receiving treatment for acute HIV infection and resumed ART when VL reached >5000 copies/mL for 3 consecutive weeks or ≥50,000 copies/mL at a single time point. At the time of publication of the study results, 5 of the 8 patients had not resumed ART and had VLs of <500 copies/mL after a median of 6.5 months. All demonstrated increased HIV-specific cytotoxic T lymphocyte counts and maintained T helper cell responses.

A later study with patients receiving treatment for acute HIV infection (N = 14), which included patients from the study by Rosenberg et al. [63] and used the same VL thresholds for resuming ART, found that virologic control, in general, did not persist while therapy was discontinued [64]. Less than half of the patients (43% [6 of 11]) retained VLs of <5000 copies/mL for 1 year after stopping therapy, and less than a quarter of the patients (21% [3 of 14]) had VLs that remained below the threshold for 2 years after therapy cessation. Loss of viral control occurred despite increased HIV-specific immune responses.

Chronic infection. A recent study reported some virologic
benefit from structured treatment interruptions intended to stimulate host immunity in chronic HIV infection. Patients were randomized to continue receiving ART, structured treatment interruption, immunization (ALVAC-HIV vCP1452), or structured treatment interruption plus immunization (N = 97; VL, <50 copies/mL; CD4 cell count, >400 cells/μL) [65]. Patients in the 2 structured treatment interruption arms demonstrated better virologic control, measured as a significantly lower median peak VL (5.36 [95% CI, 4.58–5.79] vs. 4.73 [95% CI, 4.07–4.91] log10 copies/mL; P = .0002) and a significantly longer median doubling time to initial VL increase (1.95 [95% CI, 1.25–2.96] vs. 2.48 [95% CI, 1.85–3.63] days). Effects were modest but offer limited evidence that structured treatment interruptions can affect markers of viral replication. These potential benefits, however, must be balanced against the risk of resistance and the risk of clinical events.

CONCLUSIONS

New antiretroviral drug classes and new ARVs in existing classes offer the promise of continued improvements in virologic efficacy, even for triple-drug-class–experienced patients and those with MDR HIV strains. Given the relatively slow rate at which mutations develop in highly treatment-experienced patients and the importance of including ≥2 active ARVs in a new regimen, it is reasonable to delay switching from a partially suppressive ART while the patient is clinically stable and a regimen containing ≥2 fully active ARVs cannot be constructed.

Resistance testing should be done for patients with acute infection (especially if therapy is initiated at this stage); for patients with chronic infection before ART is started; during pregnancy, if the mother is viremic; and for patients experiencing virologic failure. The prevalence of transmitted resistance ranges from 5% to 15% among ART-naïve patients. Triple-drug-class resistance is common among treatment-experienced patients, but the incidence of new triple-drug-class resistance appears relatively low among chronically infected patients who are first treated with cART.

Structured treatment interruptions should not be used to reduce drug exposure and toxicity, since this practice has been linked to increased rates of death and disease progression; the latter includes non–HIV-related events. Structured treatment interruptions for highly treatment-experienced patients, to reseensitize HIV-1 to antiretroviral drugs, does not improve treatment outcomes and may increase the risk of disease progression.

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