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HIV-1 Treatment-Experienced Patients: Treatment Options and Management

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1. Introduction

Human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) are a global health crisis of unprecedented dimensions, causing over 25 million deaths worldwide since it was first recognized as a disease entity in the early 1980s.(Joint United Nations Program on HIV/AIDS 2008) In 2008 alone, there were approximately 2.7 million newly infected and over 33 million persons living with HIV globally, of whom between 1.8 and 2.3 million died.(Joint United Nations Program on HIV/AIDS 2011) In the 24 years since zidovudine was approved for the treatment of HIV infection, remarkable advances have been made in the understanding of disease pathogenesis and translating that knowledge into practical therapeutics. Most notably, the advent of highly active antiretroviral therapy (HAART) has transformed HIV from an inevitably fatal disease to one that, if managed appropriately, can be considered a chronic condition. As a result, the overall number of people living with HIV is increasing as these regimens extend life and as new infections outnumber AIDS deaths. (www.unaids.org; Joint United Nations Program on HIV/AIDS 2011)

The number of HIV treatment regimens has grown exponentially, particularly in the past decade. This, coupled with advances in the understanding of disease pathogenesis and progression, has made HIV disease management among the most dynamic fields in modern medicine. A number of guidelines have been developed to assist practitioners with often complex treatment decisions. These include the 2010 International AIDS Society (IAS/IAS-USA) guidelines and the 2011 US Department of Health and Human Services (DHHS) HIV treatment guidelines.(Thompson, et al., 2010; http//:www.aidsinfo.nih.gov; Thompson, et al., 2010; United States Department of Health and Human Services (US DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents 2011)

Close to 30 individual drugs and fixed-dose combinations are available to treat HIV. Despite the availability of a broad range of individual antiretroviral treatments and combinations, drug resistance remains a common phenomenon, and treatment failure is still frequently observed. Moreover, treatment advances—together with recent demographic shifts—have resulted in a dramatic expansion in the population of treatment-experienced patients. This group comprises an ever-increasing proportion of the patients whom HIV clinicians are called upon to treat. This review attempts to integrate guideline recommendations and evidence from recent clinical trials to identify best practices in the management of these patients.

2. The treatment-experienced patient

According to the IAS, the primary goal of antiretroviral therapy is to increase disease-free survival through the maximal suppression of viral replication and preservation of immunologic function.(Thompson, et al., 2010; Hammer, et al., 2008) Optimal therapy for patients with HIV depends on carefully balancing these benefits with the risks for drug toxicity, potential emergence of viral resistance, and the understanding that HIV infection is a chronic disease that requires continuous therapy—often for decades. These considerations are complicated in the treatment-experienced patient, as these patients often have accumulated resistance mutations to a number of drugs in existing antiretroviral drug classes. Modifications of treatment regimens may be forced by undue toxicity, drug-drug interactions, or outright virologic failure. While, theoretically, it is optimal for patients to remain on a single treatment until virologic failure, regimens may also be modified to improve convenience and/or ameliorate minor or cosmetic side effects, ultimately improving adherence and increasing time to virologic failure.(Thompson, et al., 2010; Hammer, et al. 2008)

3. Defining treatment failure

Treatment failure may be defined based on HIV RNA response to therapy (virologic failure), changes in CD4+ cell count (immunologic failure), and the occurrence or recurrence of HIV-related events after ≥ 3 months on an antiretroviral regimen (clinical progression). (US Department of Health and Human Services (DHHS) Panel on Antiretroviral treatment guidelines for adults and adolescents 2011, http://aidsinfor.nih.gov)

Virologic failure may be characterized as persistent HIV RNA viral load above 200 copies/mL. (US DHHS HIV treatment guidelines 2011) Occasional episodes of viral detection between 51 and 1000 copies/mL may occur due to laboratory variation or other transient viral illness. However, frequent and/or consistent viremia is a strong indicator of treatment failure and must be addressed to prevent selection of drug-resistant virus.

Immunologic failure is the failure to achieve and maintain an adequate CD4+ T-cell response despite virologic suppression. Although an absolute definition has not been agreed upon by experts, immunologic failure can generally be considered as failure to increase CD4+ cell counts above 350−500 cells/mm^3 over 4−7 years of treatment.(US DHHS HIV treatment guidelines 2011) Alternatively, it may be defined as failure to increase CD4+ cell count by 50−100 cells/mm^3 above baseline during the first year of a new therapy, or a decline in CD4+ cell count to below baseline while on therapy.(US DHHS HIV treatment guidelines 2011)

Clinical progression is the occurrence or recurrence of HIV-related conditions (a new AIDS defining illness or death) after ≥3 months of HAART, excluding immune reconstitution syndromes.(US DHHS HIV treatment guidelines 2011)

While virologic failure, immunologic failure, and clinical progression are closely related, all three may not occur simultaneously. In general, virologic failure precedes immunologic failure and clinical progression of disease; however, the period between overt virologic failure and detectable suppression of CD4+ cell count and/or HIV-related events can span from months to years.(US DHHS HIV treatment guidelines 2011; Deeks, et al., AIDS 2002)

4. Assessing treatment failure

In general, treatment failure cannot be attributed to any single cause. When assessing individual patients with treatment failure, it is important to recognize that multiple reasons for failure may occur in a single patient. These include:

1. patient-specific factors, such as earlier calendar year of starting therapy, high baseline HIV RNA level, lower nadir CD4+ cell count, prior AIDS diagnosis, the presence of comorbidities such as depression or active substance use, and infection with a drug-resistant virus;
2. medication noncompliance and/or missed clinic appointments;
3. medication side effects and toxicity, potentially leading to noncompliance;
4. suboptimal pharmacokinetics, including variable absorption, metabolism, penetration, food/fasting requirements, and drug and natural product interactions; and
5. suboptimal potency of the antiretroviral regimen.(http://aidsinfo.nih.gov)

Of these reasons, suboptimal adherence and toxicities account for the majority (26%−64%) of treatment failures and discontinuations.(d'Arminio Monforte, et al. AIDS 2000; Mocroft A, et al. AIDS 2001)

5. Addressing treatment failure

Careful assessment of the reasons for treatment failure is critical, as approaches to subsequent therapy differ based on the combination of risk factors in the individual patient. Of the potential reasons for failure summarized above, all except certain patient-specific risk factors can be addressed through appropriate attention to maintaining adherence (either to the current regimen or to a new regimen) and careful assessment of all of the patients' current medications, including but not limited to HAART, treatments for comorbid conditions, and natural health products.

5.1 Noncompliance

Unless the patient was infected with resistant virus, treatment failure implies inadequate adherence to antiretroviral therapy. The development of drug resistance requires concurrent antiretroviral drug exposure and ongoing viral replication. Thus, even intermediate adherence (e.g., 70%−90% compliance) is associated with considerable risk for the development of drug-resistant strains of HIV, as a result of ongoing low-level drug exposure and intermittent viral replication. (Lucas GM, et al., J Antimicrob Chemother 2005) For this reason, it is worthwhile to target 90%−100% compliance in patients with HIV.

The causes of nonadherence must be identified and addressed in cooperation with the patient to avoid future treatment failures and the accumulation of drug-resistance mutations. Numerous reasons for nonadherence to medication have been described in the literature. These include, but are not limited to, regimen complexity (a particular problem in HIV treatment), (Ammassari, et al., Neurology 2003) side effects, (Ammassari, et al., JAIDS 2001) failure to understand dosing directions, illiteracy,(Kalichman, et al., J Natl Med Assoc 1999) substance abuse, (Power , et al., AIDS Pt Care STDS 2003) psychological issues, (Gibbie, et al., Sex Health 2007) cost, missed appointments, and lack of social supports..

Routinely discussing adherence with patients at each visit may improve medication adherence. Pill boxes are helpful for patients who are busy or forgetful and have the additional benefit of being highly cost-effective. In one study, its use resulted in a significant

4% improvement in adherence that correlated with a significant reduction in viral load. (Petersen M, et al. CROI 2007)

5.2 Side effects and toxicities

When treatment fails, the patient should be carefully assessed for side effects and their duration and severity. In some cases, side effects are transiently associated with the initiation of a new regimen. However, ongoing side effects should first be managed, if possible, by using symptomatic treatment (e.g., antiemetics and antidiarrheals). Alternatively, substitution of one drug for another in the same therapeutic class may reduce symptoms. For example, tenofovir or abacavir may be used to replace zidovudine in patients with gastrointestinal symptoms or anemia.(US DHHS HIV treatment guidelines 2011) Changing drug classes altogether is also an option in patients who experience side effects with multiple alternative drugs within the same class.

5.3 Pharmacokinetic parameters

The risk for treatment failure is increased if the patient is not taking the medication correctly (e.g., with or without food and otherwise, as directed). Similarly, treatment may fail if the patient is taking other medications, prescription or over the counter, that may affect drug absorption or metabolism (e.g., proton pump inhibitors).

The effect of natural health products, such as herbs and vitamins, is underappreciated as a source of potentially detrimental interactions with antiretroviral treatment. Data suggest that more than two thirds of HIV patients take natural or alternative health products, (Rivera, et al., J Natl Med Assoc 2005) and that many physicians are not aware of their patients' use of "natural" or alternative health products. The complexities of accounting for interactions between these products and antiretroviral treatments are compounded by the fact that natural health products are not produced to a generally accepted standard, and there may be wide variability in potency between and within brands. Moreover, many natural health products are complex mixtures that may contain components that influence drug metabolizing enzymes and drug transporters.(Lee LS, et al. CID 2006) Table 1 presents some known interactions between antiretroviral drugs and natural health products.

5.4 Drug resistance

When noncompliance, side effects and toxicities, and potential pharmacokinetic interactions have been excluded, drug resistance should be considered. Resistance testing should be performed while the patient is still on the failing regimen or within 4 weeks of discontinuation, and before starting a new regimen. In general, changing therapy for virologic failure is warranted for detectable viremia >1000 copies/mL. Some authorities suggest a more aggressive approach, in which therapy is changed for any repeated, detectable viremia (e.g., two consecutive HIV RNA >50 copies/mL after suppression to <50 copies/mL in a patient receiving antiretroviral treatment), but this is not routine practice.(http://aidsinfo.nih.gov)

5.4.1 Drug resistance testing

Resistance testing may be accomplished through genotype or phenotype testing. Two types of resistance assays are available in clinical practice. Genotypic assays involve sequencing HIV-1 genes to detect mutations that confer HIV-1 drug resistance, whereas phenotypic assays use cell-culture based viral replication assays in the presence and absence of drugs.

	St. John's wort	*Echinacea*	*Milk thistle*	*Garlic*	*Vitamin E*
PIs	Should not be coadministered; may cause significant decrease in PI levels	Possible interaction; echinacea may interact with ARVs that are CYP 3A4 or CYP 2C9 substrates	Possible interaction, except for indinavir; milk thistle may inhibit CYP3A4	Possible interaction; garlic may inhibit CYP3A4 GI toxicity has been reported with coadministration of garlic and ritonavir	Should not be coadministered with tipranavir/ritonavir; may increase the risk of bleeding
NNRTIs	Should not be coadministered; may cause significant decrease in NNRTI levels (including etravirine)	Possible interaction; echinacea may interact with ARVs that are CYP 3A4 or CYP 2C9 substrates	Possible interaction; milk thistle may inhibit CYP 3A4	Possible interaction; garlic may inhibit CYP 3A4	Unknown
NRTIs	No evidence for interaction	No evidence for interaction	No evidence for interaction	No evidence for interaction	No evidence for interaction
Integrase inhibitor (raltegravir)	No evidence for interaction	No evidence for interaction	No evidence for interaction	No evidence for interaction	No evidence for interaction
CCR5 antagonist (maraviroc)	Coadministration not recommended; expected to decrease maraviroc concentrations	Possible interaction; echinacea may interact with ARVs that are CYP 3A4 and CYP 2C9 substrates	Possible interaction; milk thistle may inhibit CYP 3A4	Possible interaction; garlic may inhibit CYP 3A4	No evidence for interaction

Table 1. Known Interactions Between Antiretroviral (ARV) Therapies and Natural Health Products
CYP, cytochrome P; GI, gastrointestinal; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
(Reyataz, Intelence, Aptivus, & Selzentry package inserts; Gorski, et al., 2004; Mills, et al., 2005; Venkataramanan, et al., 2000; Foster, et al., 2001; Laroche, et al., 1998; Lee, et al., 2006)

Both tests can accurately identify resistance only in the predominant virus in patients, so a substantial proportion of the circulating virus may be resistant even in patients with negative results.(Schuurman, et al., J Clin Microbiol 1999) Furthermore, drug resistance testing is limited, because it does not predict the activity of antiretroviral agents when used in combination and requires a viral load >1000. Also, it only reveals resistance based on drug pressure, so it is important to consider all prior genotype tests, as these mutations will remain, even if not currently detectable. In addition to these methods, "virtual phenotyping" utilizes

genotype data to evaluate *in vitro* drug susceptibility of the virus; for most antiretroviral agents, this test predicts actual phenotypic resistance.(Perez-Elias, et al., Antivir Ther 2003)
Despite limitations, the preponderance of evidence suggests an advantage for the use of genotypic testing over standard of care in the selection of regimens for patients with treatment failure.(Hirsch, et al., CID 2003) Compared with standard of care, the patients allocated to the genotyping arms of these studies had substantially greater decreases in plasma HIV RNA levels and were more likely to achieve undetectable HIV RNA levels. In contrast, trials of phenotypic testing versus standard of care have not produced such clear-cut results, with variable outcomes in different studies. (Hirsch, CID 2003; Melnick, et al., abstract #786 CROI 2000; Cohen, et al., AIDS 2002; Torti, et al., CID 2005; Dunn, et al., JAIDS, 2005; Vray, et al., 2003; Wegner, et al., CID 2004). A recent clinical study compared outcomes in patients randomly assigned to either genotypic testing or genotypic plus virtual phenotypic testing. (Hales, et al, PLoS Clin Trials 2006) After 48 weeks, no significant differences were observed between the two groups in terms of mean change from baseline plasma HIV RNA and mean change from baseline CD4+ cell count, suggesting that resistance testing with genotyping alone is sufficient for the management of HIV infection. Tables 2, 3, and 4 indicate resistance mutations for the three major classes of antiretrovirals.

6. 2011 Guidelines for the management of treatment-experienced patients

When selecting appropriate treatment, all resistance testing should be considered, as should the patient's treatment history, comorbidities, concomitant medications, and prior intolerance. Treatment should be individualized based on these factors.
In patients with limited prior treatment but with no resistance, the potential for nonadherence should be evaluated and strongly considered. Resumption of the same regimen or initiation of a new regimen should be considered, with genotypic testing within 4 - 6 weeks to determine whether a resistant viral strain emerges if viral suppression cannot be achieved. In patients with limited prior treatment who are receiving protease inhibitors (PIs), thought should be given to intensifying one drug or boosting. The primary goal of therapy is to resuppress HIV RNA levels to undetectable levels and to prevent further selection of resistance mutations. (http://aidsinfo.nih.gov)
In patients with limited prior treatment and recognized drug resistance, maximal HIV RNA suppression (e.g., to <50 copies/mL) is required to prevent the selection of additional resistance mutations. (Thompson, et al, 2010; http://aidsinfo.nih.gov) Changes in the treatment regimen should be considered to minimize selection of resistance mutations. New regimens should include ≥2 active agents. (Thompson, et al, 2010; http://aidsinfo.nih.gov)
Resistance mutations for nucleoside analog reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), and PIs are noted in Tables 2, 3, and 4, respectively. Effects of Protease mutations are noted in Table 5.
In patients with extensive prior treatment and drug resistance, maximal viral suppression is warranted to prevent the accumulation of additional resistance mutations. Antiretroviral drugs from newer classes should be considered. If viral suppression is impossible to achieve, the primary goal is to preserve immunologic function and prevent clinical progression. When a new regimen with two fully active agents cannot be identified, it is reasonable to observe the patient on the same regimen rather than changing the regimen, depending on the stage of HIV disease. (Thompson, et al, 2010; http://aidsinfo.nih.gov)
Patients with significant treatment experience and drug-resistant virus can often still achieve undetectable viral loads and the goal is still to reestablish suppression of the virus.

NRTI	*Resistance mutations* (IAS-USA)	*Mutations associated with reduced* RC
All currently approved NRTIs	69 insertion complex: M41L, A62V, 69 insert, K70R, L210W, T215Y/F, K219Q/E	
All currently approved NRTIs except tenofovir	151 complex: A62V, V75I, F77L, F116Y, Q151M	Q151M
All currently approved NRTIs	Thymidine analogue-associated mutations (TAMs): M41L, D67N, K70R, L210W, T215Y/F, K219Q/E	
Abacavir	K65R, L74V, Y115F, M184V	K65R, M184V
Didanosine	K65R, L74V	K65R
Emtricitabine	K65R, M184V/I	K65R, M184V
Lamivudine	K65R, M184V/I	K65R, M184V
Stavudine	M41L, D67N, K70R, L210W, T215Y/F, K219O/E	
Tenofovir	K65R, K70E	K65R
Zidovudine	M41L, D67N, K70R, L10W, T215Y/F, K219Q/E	

Table 2. NRTI resistance mutations
IAS, International Aids Society; NRTI, nucleoside reverse transcriptase inhibitor; RC, replicative capacity.
(Johnson, et al., 2009; Garcia-Perez, et al., 2005; Girardet, et al., 2007; White, et al., 2002)

NNRTI	*Resistance mutations* (IAS-USA)	*Mutations associated with reduced* RC
Delavirdine	K103N, V106M, Y181C, Y188L, P236L	V106A, G190C/S/E/Q/V/T, P225H, M230L, and P236L
Efavirenz	L100I, K103N, V106M, V108I, Y181C/I, Y188L, G190S/A, P225H	V106A, G190C/S/E/Q/V/T, P225H, M230L, and P236L
Nevirapine	L100I, K103N, V106A/M, V108I, Y181C/I, Y188C/L/H, G190A	V106A, G190C/S/E/Q/V/T, P225H, M230L, and P236L

Table 3. NNRTI Resistance Mutations
NNRTI, non-nucleoside reverse transcriptase inhibitor; RC, replicative capacity.
(Johnson, et al., 2009; Archer, et al., 2000; Huang, et al., 2003; Wirden, et al., 2003)

(US DHHS HIV management guidelines) NRTIs, in particular, have been shown to retain antiviral activity in patients with drug-resistant virus. Moreover, continued use of both NRTIs and PIs can select for drug-resistance mutations that reduce viral fitness. (Deeks, et al., 2005)
If complete viral suppression is not feasible, the goals of treatment should be maintenance or improvement of CD4+ cell count and preventing clinical progression. Discontinuation is not recommended unless the patient has a high CD4+ count. Data suggest that partial virologic suppression of >0.5 to 1.0 $\log_{10}$ copies/mL below baseline is associated with clinical benefit; larger and more sustained reductions in HIV RNA are directly correlated with lower risk for disease progression. (Murray, et al., 1999) In addition, a "holding regimen" will maintain poor viral fitness. For example, the M184V mutation, which increases resistance to lamivudine and emtricitabine, decreases viral fitness and increases

the antiviral activity of zidovudine, stavudine, and tenofovir. (Whitcomb, et al., 2003) Therefore, maintaining this resistance mutation by continuing lamivudine or emtricitabine can enhance the effect of zidovudine, stavudine, and/or tenofovir. (Wegner, et al., CID 2004)

Protease inhibitor	*Major resistance mutations* (IAS-USA)	*Mutations associated with reduced* RC
Atazanavir +/- ritonavir	I50L, I84V, N88S	I50L
Fosamprenavir/ritonavir	I50V, I84V	I50V, I84V
Darunavir/ritonavir	I47V, I50V, I54M/L, L76V, I84V	
Indinavir/ritonavir	M46I/L, V82A/F/T, I84V	
Lopinavir/ritonavir	V32I, I47V/A, L76V, V82A/F/T/S	
Nelfinavir	D30N, L90M	D30N, N88S, L90M
Saquinavir/ritonavir	G48V, L90M	
Tipranavir/ritonavir	I47V, Q58E, T74P, V82L/T, I84V	

Table 4. Major Protease Inhibitor Resistance Mutations
IAS, International Aids Society; RC, replicative capacity.
(Johnson, et al., 2009; Archer, et al., 2000; Martinez-Picado, et al., 1999; Prado, et al., 2002; Resch, et al., 2002; Wirden, et al., 2003; Reyataz prescribing information)

In some highly treatment-experienced patients, the addition of enfuvirtide should also be considered. In the T-20 versus Optimized Regimen Only (TORO) studies, adding enfuvirtide to an optimized background regimen was associated with significant antiretroviral and immunologic benefit in patients with >6 months of previous treatment with agents in three classes of antiretroviral drugs and/or resistance to drugs in these classes.(Lalezari, et al., 2003) Notably, enfuvirtide is most effective when given with other active drugs. As shown in the TORO study, enfuvirtide monotherapy is associated with a high rate of emerging resistance. (Lalezari, et al., 2003)
DHHS guidelines indicate no consensus on how to define or treat immunologic failure in the setting of a virologic response. (US DHHS HIV management guidelines) Patients with discordant responses (e.g., undetectable HIV RNA but low CD4+ cell counts) should continue to receive their current treatment, unless they are taking zidovudine or didanosine, which have been shown to be myelosuppressive. However, time to immune response is variable and may even take years. In these cases, changing these drugs, if possible, is recommended. Additionally, changing trimethoprim-sulfamethoxazole prophylaxis to dapsone or aerosolized pentamidine may be warranted in this group in order to enhance immunologic response further. This should be considered prior to changing an antiretroviral regimen that is successfully suppressing viral load.

7. Beyond the guidelines: Investigational therapeutic approaches

Numerous permutations of various treatment strategies have been attempted. Below are several of the more commonly investigated therapeutic approaches.

7.1 Structured treatment interruptions

The CPCRA 064 study found that there was an increased risk of death, a long-term negative effect on CD4+ cell count, and no virologic or clinical benefit associated with a structured

treatment interruption.(Lawrence, et al., 2006) Based on these, it is advised to not discontinue an ARV regimen in an adherent patient except for in the presence of drug resistance and when awaiting genotype results.

7.2 Double-boosted PIs

Double-boosted PIs (two PIs plus ritonavir) may be clinically effective by increasing blood levels to the point where resistance is overcome.(Staszewski, et al., 2006) This approach raises major issues, however, in terms of drug interactions and may be suitable only for patients who have exhausted all other options. This is not strongly advised or recommended and the patient should be referred to an HIV specialist.

7.3 Mega-HAART

Multiple-drug rescue therapy (e.g., >5 antiretrovirals) has the complication of severe drug interactions. Thus, this is a last resort in highly selected patients and should be managed by an HIV specialist.(Montaner, et al., 2001)

8. New treatment options

Over the past 3 years, a number of new treatment options have been approved by the US Food and Drug Administration, including drugs from entirely new classes: maraviroc, a CCR5 antagonist, and raltegravir, an integrase inhibitor. Drug interactions of these newly approved agents are summarized in Table 6.

Effect	TPV	LPV	ATV	DRV
Decreased virologic response	no firm data	6 or more mutations	Increasing number of mutations	I47V, I54M, T74P, I84V
High level resistance	no firm data	7 – 8 mutations; I47A, V32I; L76V+3 mutations	I50L, I84V, N88S	3+of: V11I, V32I, L33F, I47V, I50V I54M/L, G73S, L76V, I84V, L89V
Possible increased virologic response	L24I, I50L/V, F53Y/L/W, I54L, L76V		M46I + L76V without other mutations	V82A

Table 5. Impact of Protease Inhibitor Resistance Mutations: Effects of different PI mutations on different PIs

*ATV, atazanavir; DRV, darunavir; LPV, lopinavir; TPV, tipranavir. PI, Protease Inhibitor (Norton, et al., 2008; DeMeyer, et al., 2009; Descamps, et al., 2009; Mo, et al., 2005; Friend, et al., 2004; Kagan, et al., 2005; Rhee, et al., 2010; Schapiro, et al., 2010, and Marcelin, et al., 2008; all as cited by Johnson, et al., 2010)

8.1 Newer protease inhibitors

In the RESIST-1 and RESIST-2 trials (Randomized Evaluation of Strategic Intervention in Multidrug Resistant Patients with Tipranavir), tipranavir-ritonavir plus optimized best regimen provided superior virologic and immunologic responses over 48 weeks compared

with patients who received an investigator-selected ritonavir-boosted comparator PI plus optimized background regimen. (Hicks, et al., 2006) Gastrointestinal disorders, transaminitis, and hyperlipidemia were more frequent in patients who received tipranavir-ritonavir compared with the control group. Tipranavir carries black-box warnings regarding the risk for hepatitis and hepatic decompensation as well as fatal and non-fatal intracranial hemorrhage. (Aptivus package insert, Boehringer Ingelheim Pharmaceuticals 2008) Tipranavir's unique resistance profile makes it valuable in patients who have failed prior PI-containing regimens. (Marcelin, et al., 2008) Tipranavir is approved for highly treatment-experienced HIV patients or those with multiple PI resistance mutations.
Ritonavir-boosted darunavir has shown superiority to boosted comparator PIs in treatment-experienced patients, including those with PI mutations. (Clotet, et al., 2007) The POWER 1, POWER 2, and POWER 3 (Performance Of TMC114/r When evaluated in treatment-Experienced patients with PI Resistance) studies found 40%−44% attained viral suppression among treatment-experienced patients who had previously failed other PI-based regimens. Thus, darunavir is also valuable in patients with significant resistance. (Lefebvre, et al., Abstract H-1387, ICAAC 2006) Darunavir is approved for both treatment-experienced and treatment-naïve patients. Table 5 shows the impact of protease mutations on resistance to various PIs.

8.2 New non-NRTI

The DUET 1 and 2 (TMC125-0216: a phase 3 study to investigate the efficacy, tolerability, and safety of TMC125(etravirine) as part of an antiretroviral regimen, with optimized background regimen in HIV-1 infected patients with limited to no treatment options) trials examined the efficacy of etravirine, a second-generation NNRTI, in treatment-experienced adult patients with virological failure on stable antiretroviral therapy and documented genotypic evidence of NNRTI resistance, viral load >5000 copies/mL, and ≥3 primary PI mutations.(Lazzarin, et al., 2007; Madruga, et al., 2007) Etravirine was associated with superior virologic suppression compared with placebo, with up to 62% of patients in the etravirine group achieving undetectable viral loads, compared with 44% in the placebo group. (Lazzarin, et al., 2007; Madruga, et al., 2007) Etravirine exhibits retained activity despite multiple NNRTI mutations, with high rates of sustained efficacy at 48 weeks in heavily treatment-experienced patients. (Haubrich, et al, Abstract #790, CROI 2008; Johnson M, et al., Abstract #792, CROI, 2008) The tolerability profile is comparable to placebo, with the exception of a rash. It is associated with significant drug interactions and should not be used with unboosted PIs, boosted atazanavir, fosamprenavir, tipranavir, or other NNRTIs.[49](Intelence package insert, Tibotech Therapeutics 2008) The mutation Y181 decreases susceptibility to etravirine, but does not eliminate efficacy altogether. (Johnson, et al, 2010; http://aidsinfo.nih.gov)

8.3 New class: CCR5 antagonist

Maraviroc, the first drug in this class to be licensed, is active against chemokine receptor R5- but not X4-tropic viruses in vitro. In the MOTIVATE 1 and MOTIVATE 2 (Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients) trials, patients who had R5-tropic virus and had been treated with or had resistance to three antiretroviral drug classes, and had HIV RNA >5000 copies/mL, demonstrated increased CD4+ counts and more sustained viral suppression at 48 weeks following treatment with maraviroc compared with placebo, and with comparable adverse event outcomes. (Gulick, et al., 2008) Maraviroc is not effective in patients with mixed-tropic virus infection; it is

indicated for the treatment of patients infected with only CCR5-tropic HIV who are either treatment naïve, or who have evidence of viral replication and HIV strains resistant to multiple antiretroviral agents.(Selzentry package insert, Pfizer, Inc.) Patients that may benefit from having a regimen including maraviroc can be identified via any of several assays available to assess the presence of the CCR5 tropic virus and the minority CXCR4 (X4) strains. (Reeves, et al., Abstract H-1026, ICAAC, 2007)

8.4 New class: Integrase inhibitor

Raltegravir, the first-in-class integrase inhibitor, was examined in combination with optimized background regimen in two identical, placebo-controlled trials in patients infected with triple-class drug-resistant HIV-1 in whom antiretroviral therapy had failed. (Steigbigel, et al., 2008) At 48 weeks of therapy, 62.1% and 32.9% of raltegravir and placebo patients, respectively, had suppressed HIV RNA viral load. Raltegravir is approved in combination with other antiretroviral agents for the treatment of HIV infection in treatment-naïve or treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. (Isentress package insert, Merck & Co)

9. Drugs under investigation

A new integrase inhibitor, Dolutegravir (Glaxo Smith Kline) is in phase 2 clinical trials and is active against raltegravir-resistant strains, revealing a higher genetic barrier to resistance (Seki, et al., abstract #555, CROI 2010; Eron, et al., abstract #151LB, CROI 2011).

GSK2248761 is a once daily NNRTI currently in phase 2b studies with activity against virus with many NNRTI mutations, including efavirenz resistant strains. (Kim, et al., abstract #628, CROI 2011; Kim, et al., abstract #631, CROI 2011) In addition, this drug appears to have an additive to synergistic antiviral effect when coadministered with other antiretrovirals. (Vavro, et al. abstract #520, CROI 2011)

BI-C is a non-cataytic site integrase inhibitor that may have activity against virus resistant to other integrase inhibitors. It has shown very good biological and pharmacological profiles and is now in Phase 1 clinical trials. (Fenwick, et al., abstract #523, CROI 2011)

9.1 New classes(future)

These are not currently approved and have yet to start Phase 3 clinical trials, however, they show promise as potential future new drug classes. Their possible addition to the current arsenal of antiretrovirals is particularly important for the treatment experienced patient.

9.1.1 Attachment inhibitors

Currently in very early trials, this class shows the possibility for potent antiretroviral activity against HIV-1 infection. (Nettles, et al., abstract #49, CROI 2011). New targets include the gp 120 glycoprotein, which allows attachment of virus to CD4+ cells. (Nowicka-Sans, et al., abstract #518, CROI 2011)

9.1.2 Gag inhibitors

Another potentially new class of antiviral drugs being investigated are gag inhibitors. This drug targets the HIV-1 capsid and exhibited inhibition of the early phase of its life cycle. (Urano, et al., abstract #525, CROI 2011)

	Interactions with other ARVs	*Selected interactions with non-ARV drugs*
Etravirine	Should not be coadministered with: • Tipranavir/ritonavir • Fosamprenavir/ritonavir • Atazanavir/ritonavir • Unboosted PIs • NNRTIs Dose adjustment not established with Saquinavir, consider Saquinavir 1000mg bid + Ritonavir 100mg bid If with Maraviroc: MVC 600mg bid MVC 150mg bid (if with Ritonavir boosted darunavir)	Drug concentration monitoring recommended when used with antiarrythmics INR monitoring recommended when used with warfarin; clopidogrel should not be coadministered Certain anticonvulsants, including carabamazepine, phenobarbital, and phenytoin, can cause significant decreases in etravirine plasma concentrations Dose adjustments may be necessary for coadministration with itraconazole, ketoconazole, voriconazole; coadminister with caution and follow drug levels Clarithromycin alternatives should be considered Rifampin, rifapentine, and rifabutin may cause significant decreases in etravirine plasma concentrations Etravirine may increase plasma concentrations of diazepam , dose adjustment may be necessary Dexamethasone should be used with caution, as etravirine levels may decrease. Interaction with certain statins has been detected Etravirine may be coadministered with methadone; however, clinical monitoring for withdrawal symptoms is recommended, as methadone maintenance therapy may need to be adjusted Administer with immunosuppressants with caution; levels of cyclosporine, tacrolimus, and sirolimus may be decreased
Raltegravir	No effect expected on the following drug classes: PIs, NNRTIs that would	No effect expected on methadone, opioid analgesics, statins, azole antifungals,

	require dose adjustments	proton pump inhibitors, oral contraceptives, anti-erectile dysfunction agents
	No clinically meaningful effect on lamivudine, tenofovir	Caution recommended when coadministering with rifampin; reduces plasma concentrations of raltegravir
	Recommended dose of raltegravir may be coadministered with efavirenz, nevirapine	Recommended dose of raltegravir may be coadministered with rifabutin ; recommend 800 mg twice daily with coadministered rifampin
	Recommended dose of raltegravir may be coadministered with boosted tipranavir or atazanavir	
Maraviroc	Dose reduction to 150 mg twice daily with PIs (except tipranavir/ritonavir), delaviridine	Dose reduction to 150 mg twice daily with ketoconazole, itraconazole, clarithromycin, other strong CYP 3A inhibitors (e.g., nefazadone, telithromycin)
	No dose adjustment (300 mg twice daily) with tipranavir/ritonavir, nevirapine, NRTIs	Dose increase to 600 mg twice daily with CYP 3A inducers including rifampin, carbamazepine, phenobarbital, phenytoin
	Dose increase to 600 mg twice daily with CYP 3A inducers including efavirenz	No clinically relevant effect on midazolam, oral contraceptives (ethinylestradiol and levonorgestrel)
	No effect on zidovudine, lamivudine	

Table 6. Drug Interactions of Newly Approved Antiretroviral Therapies
ARV, antiretroviral; INR, International Normalized Ratio; CYP, cytochrome; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
(Aptivus, Invirase, Isentress, Kaletra, Lexiva, Prezista, Reyataz, Selzentry, Sustiva, Viracept, and Viramune prescribing information)

10. Conclusion

Managing treatment-experienced patients poses considerable challenges, not the least of which includes selecting appropriate therapy to maximize clinical benefit, minimize toxicities, and avoid drug-drug interactions. The best approach to these patients is preventative. As noted above, with appropriate attention to medication adherence and addressing the side effects and toxicities of antiretroviral medications proactively, many patients can remain on the first regimen for many years. In the real world, however, a substantial proportion of patients fail to adhere to their medication. Many suffer from overt toxicities and/or minor/cosmetic side effects that affect compliance with treatment and eventually necessitate a switch in regimen. Given the broad spectrum of available agents—including the recent advent of two entirely new classes of antiretroviral agents—the majority of patients have reasonably well-tolerated therapeutic options that, with appropriate attention to all aspects of the clinical and patient experience, can provide sufficient long-term efficacy which has transformed HIV from an inevitably fatal disease to one that can truly be considered a chronic condition.

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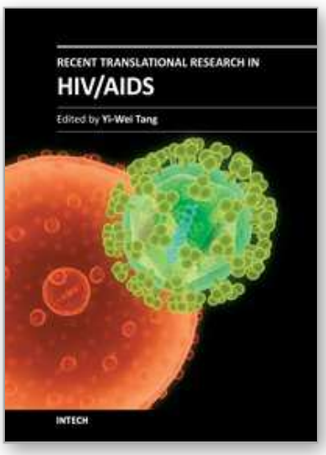

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