

Overview of Antiretroviral Therapy

Paul A. Volberding

Introduction

Antiretroviral (ARV) therapy is one of the most dramatic examples of successful drug development in the history of medicine. ARV therapy, when used appropriately, can reduce HIV replication to extremely low levels. It can allow the restoration of even advanced immune deficiency to safe levels in the vast majority of treated persons and the recovery and maintenance of health in a previously progressive and uniformly fatal syndrome. ARV can, furthermore, reduce HIV transmission and even prevent initial infection. The obvious benefits of ARV therapy realized in wealthy economies are leading to efforts to make treatment available as well in some of the world's poorest economies being devastated by the HIV epidemic.

Success in ARV therapy is not difficult, but does require substantial resources and the careful application of principles learned from clinical trials and experience from treatment program development. Drugs that form potent multi-agent regimens must be continuously available and affordable. Laboratory assays must be available to diagnose HIV infection and, ideally, to stage the illness and monitor treatment response and toxicity. Also desirable are assays used to detect ARV resistance both to improve initial response and to adjust regimens that have lost some effectiveness. Effective ARV therapy also requires access to health care providers – physicians and others – sufficiently trained to diagnose infection, to select effective drug combinations and to initiate them at the appropriate stage in HIV disease. Providers must be expert in educating patients in medica-

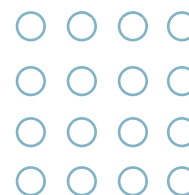
tion adherence and in managing ARV toxicity and drug interactions. They must also be able to adjust regimens to maintain clinical benefits despite drug resistance.

This chapter will provide a brief review of the biology of HIV therapy and the essential questions of ARV management including the design and timing of initial combination regimens and of secondary or salvage therapy. It will summarize current ARV drugs with respect to common toxicities, resistance patterns, and drug interactions, but will defer to other chapters that deal with many of these topics in much more detail.

The central goal of HIV therapy is suppression of viral replication sufficient to prevent the selection of drug resistance mutations.¹⁻⁴ Potent ARV regimens, however, allow some very low-level HIV replication, but not enough to result in resistance.^{5,6} Successful ARV therapy must durably restore or maintain immune competence and the control of infections and malignancies that defined the AIDS syndrome. In patients infected with HIV resistant to multiple ARV agents and even entire drug classes, therapy may not fully suppress viremia, but can still dramatically slow disease progression.^{7,8} The goal of all HIV therapy is, therefore, prolonged high quality survival making this another treatable, if not curable, chronic disease.

The Natural History of HIV Infection

Untreated HIV infection results in persisting and relatively constant levels of viremia and a



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progressive immune attrition reflected most obviously, but only in part, by a decline in the numbers of circulating CD4 positive T lymphocytes.⁹ The rate of CD4 cell loss varies widely among infected individuals but averages 60–80 cells/mm³ annually.^{10,11} Constitutional symptoms and serious infections and malignancies arise with immune attrition, particularly when the peripheral CD4 cell count falls below 200 cells/mm³. Many with initial, or acute, primary HIV infection have a one to two week clinical illness.^{12,13} Following recovery from any symptoms of this acute phase of HIV infection, most are asymptomatic until much later in the disease course, often ten or more years following infection.¹⁴ With progressing disease, some experience constitutional signs and symptoms – chronic or recurring fevers, malaise, weight loss or other evidence of chronic inflammation. Advanced HIV disease, also termed AIDS, when the CD4 cell count is below 200/mm³, is punctuated by opportunistic infections and malignancies that range from treatable inconveniences to rapidly fatal and irreversible acute illnesses. While some progress from initial infection to death in as little as 12 months, others have survived infection for more than 20 years with no apparent ill health.^{15,16}

HIV disease is staged by the CD4 cell count, with numbers above 500/mm³ considered in the normal range, while those below 200/mm³ indicate advanced disease or AIDS. As the risk of specific opportunistic diseases correlates closely with the CD4 cell count, this test is of particular value in patient management. By contrast, levels of HIV viremia are less predictive of disease stage, but may correlate with the rate of disease progression.

The HIV Life Cycle

Reviewed in detail elsewhere, a brief summary of the HIV life cycle focused on targets of existing drugs, can help in considering ARV regimen design. These targets will be considered early, middle or late in the life cycle, corresponding to currently approved ARV drugs blocking cell entry, reverse transcription or HIV protease processing.

Early Targets in the HIV Life Cycle

After the viral surface glycoprotein, gp120, and the cell surface protein, CD4, interact in attachment,¹⁷ the CD4 changes its conformation to allow the engagement into this complex of a second cell surface protein, the co-receptor, whose natural function is to act

as a chemokine receptor, either CCR5 or CXCR4.^{18–20} The CD4-gp120-chemokine receptor complex in turn activates the viral gp41 which uncoils its triple helical structure, elongates, and inserts a fusion protein into the cell surface membrane. The gp41 then returns to its tight configuration and the recoiling of gp41, now tethered to the cell, approximates the viral and cell membranes resulting in their fusion.²¹ Active drug development efforts are designing drugs to interfere with one or more points in this early life cycle phase and one, enfuvirtide, is already approved.²² This drug, a subcutaneously injected 36 amino acid polypeptide, binds to the tethered uncoiled gp41 and prevents its recoiling and thus blocks viral-cell fusion. These ‘early’ acting drugs can actually prevent cellular HIV infection, in contrast to other available ARV drugs.

Middle Targets in the HIV Life Cycle

Following membrane fusion, the viral core enters and uncoats in the target cell cytoplasm where the viral genes encoded on the single-strand HIV RNA genome are reverse transcribed into a dual-strand DNA copy.²³ The enzyme that facilitates this, reverse transcriptase, is the target of many ARV drugs, some structural analogs of normal nucleosides or nucleotides.^{24,25} Other drugs that block this enzyme, the non-nucleosides, bind to the enzyme’s active site, but have a chemical structure that does not resemble nucleosides.^{26–28} Reverse transcriptase inhibitors of both types only act following cellular infection by HIV. By convention, the nucleoside (or nucleotide) – like reverse transcriptase drugs are called the NRTIs while the non-nucleoside agents are called the NNRTIs.

Other targets in the middle phase of replication are being explored. The most active area in this focuses on HIV integrase, the enzyme that enables the incorporation of the viral genome into that of the host cell. Several HIV integrase inhibitors are in development and show real promise, but are not yet approved for use.²⁹

Late Targets in the HIV Life Cycle

As the new HIV virion forms inside the cell membrane and then buds into the extracellular environment, trimming of the structural or gag-related proteins by HIV protease is necessary for full infectivity. HIV protease inhibitors are potent ARV drugs.³⁰ Several are in use and more are being developed. Co-administration of certain HIV protease inhibitors with a low dose of ritonavir, another drug

from this class, is used to block protease inhibitor catabolism. This increases plasma drug levels and allows added potency and convenience.³¹ By convention, HIV protease inhibitors are called PIs. The co-administration of low-dose ritonavir is commonly called 'boosting.' A ritonavir boosted PI is counted as a single drug as the ritonavir dose, by itself, is sub-therapeutic. Newer drug development in the late life cycle events is targeting Gag protein maturation³² or blocking the activity of the viral gene Vif,³³ which appears to act by inhibiting innate cellular antiretroviral factors.

Elements in the Design of ARV Regimens

Achieving treatment goals, suppressing HIV replication to the lowest possible levels, currently requires the simultaneous use of multiple ARV drugs. Typically, one drug is either an NNRTI or a PI (often a boosted one). These 'cornerstone' or 'third agent' drugs are almost always combined with two NRTIs. As a boosted PI is counted as only one active drug, such regimens are often termed triple-agent ARV therapy. The use of an NRTI as a 'third drug' (thus forming a three drug NRTI combination) has been attempted but is less potent and is not a preferred option in most settings.³⁴ The choice of the two drug NRTI 'backbone' of the regimen is as important as the 'cornerstone' drug. Each drug in a typical triple drug combination must be considered on its own in terms of potency, convenience and toxicity, but the entire regimen must be similarly considered. Designing an optimum regimen must be individualized for each patient. The regimen must be compatible in terms of ease of use and tolerability for that person as its administration needs to be convenient to allow long-term medication adherence. Adverse drug interactions must be avoided and any baseline resistance mutations of each drug must be reviewed, to avoid compromised potency which can limit long-term clinical benefit.

Summarizing each ARV drug and all possible regimens of choice is beyond the scope of this review, although Table 13.1 offers a brief overview of commonly used agents. Excellent summaries of this information are included in guidelines published by national and international organizations. In the USA, both the DHHS⁴ and the IAS-USA guidelines² are frequently updated. The DHHS guidelines serve as an especially extensive information resource for many aspects of drug toxicity, potency and drug interactions. The IAS-USA also publishes updated guidelines of ARV resistance testing,³⁵ which are

extremely useful for clinical treatment planning. Other chapters in this book address HIV biology and important ARV treatment issues including drug toxicity, drug resistance, adherence, and drug interactions. These chapters should be consulted for this crucial information.

An Overview of Common ARV Regimens

Most effective ARV regimens consist of a dual NRTI 'backbone' and a third or 'cornerstone' drug.^{2,4}

Dual NRTI Backbone

Of all possible two-drug NRTI combinations, several are commonly prescribed, while others are to be avoided and yet others can be useful in specific situations affected by prior toxicity or drug resistance. Preferred combinations increasingly are co-formulations of two drugs in a single pill, increasing convenience and potentially improving medication adherence.^{36,37}

Zidovudine (ZDV) and Lamivudine (3TC)

This combination was the first to be co-formulated and, as it contains two of the first ARVs approved, has had extensive use. The main disadvantage is that it must be used twice daily. Zidovudine also can cause anemia,^{38,39} although not typically of severe grade. This combination has minimal drug interactions with other ARV drugs. The resistance barrier with zidovudine is broad, while a single mutation, M184V, confers high level lamivudine resistance. Lamivudine is also active against hepatitis B virus (HBV), but which, as a single active drug can lead to HBV resistance.^{40,41} This should be considered in designing ARV regimens for those with HBV co-infection.

Tenofovir (TDF) and Emtricitabine (FTC)

This is a newer co-formulation with less extensive clinical use. This is a potent and convenient one pill, once daily backbone. Both agents are well tolerated in short-term use. Questions of potential long-term renal or bone toxicity with tenofovir remain under investigation.⁴² Tenofovir has interactions, especially with didanosine (ddI levels increase)^{43,44} and atazanavir (ATZ levels decrease)⁴⁵ and its own levels are somewhat elevated by boosted PIs. The resistance pattern of emtricitabine is the same as lamivudine. Both drugs in this co-formulation are active against HBV although not approved for this indication. The HIV resistance pattern of tenofovir includes a K65R

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Table 13.1 Antiretroviral drugs in common use

Drug class	Generic drug name	Common abbreviation	Dose in common formulation	Dosing in adults*	Comments
Nucleoside/nucleotide Reverse Transcriptase Inhibitors (NRTI)	Zidovudine	ZDV	100 caps, 300 mg tabs (also available in two fixed dose combinations; one with lamivudine, another with both lamivudine and abacavir)	300 mg b.i.d.	Common side-effects, anemia, macrocytosis. Must be used b.i.d. Should not be used with d4T.
	Stavudine	d4T	15, 20, 30 40 mg caps	40 mg b.i.d. if >60 kg; 30 mg b.i.d. if <60 kg	Commonly causes peripheral neuropathy lipoatrophy. Lactic acidosis, pancreatitis more common when used with ddl.
	Didanosine	ddl	125, 200, 250, 400 mg EC caps	400 mg q.d. if >60 kg; 250 mg q.d. if <60 kg or if <60 kg or if used with TDF	See caution with d4T. Reduce dose when used with tenofovir.
	Lamivudine	3TC	150, 300 mg tabs	150 mg b.i.d. or 300 mg q.d.	Well tolerated.
	Abacavir	ABC	300 mg tabs (also available in two fixed dose combinations, one with lamivudine, and one with both lamivudine and zidovudine)	300 mg b.i.d. or 600 mg q.d.	Can cause rash and systemic hypersensitivity reaction that can be fatal if drug not stopped or if it is reinitiated after initial reaction.
	Tenofovir	TDF	300 mg tabs (also available in a fixed dose combination with emtricitabine)	300 mg q.d.	Combination of TDF with ddl may have reduced potency.
	Emtricitabine	FTC	200 mg caps	200 mg q.d.	Well tolerated.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)	Efavirenz	EFV	50, 100, 200 mg caps or 600 mg tabs	600 mg q.d.	Can cause rash, CNS side-effects. Both usually transient. Can cause severe teratogenicity. Take on empty stomach, usually at bedtime.
	Nevirapine	NVP	200 mg tabs	200 mg q.d. for first 14 days, then 200 mg b.i.d.	Can cause rash, hypersensitivity with hepatotoxicity; occasionally fatal.

Protease Inhibitor (PI)	Indinavir	IDV	200, 333, 400 mg caps	800 mg b.i.d. with RTV boosting dose of 100–200 mg	Hyperbilirubinemia, retinoid-like effects, renal stones, GI disorders. Should be taken with extra hydration.
	Ritonavir	RTV	100 mg caps	600 mg b.i.d. as sole PI. 100–200 mg b.i.d. or q.d. as boost for other PI.	Rarely used as sole PI as GI disorders, hyperlipidemia common.
	Saquinavir hard gel	SQV-hgc	500 mg tabs	1000 mg b.i.d. with RTV boosting dose of 100 mg b.i.d. or 400 mg b.i.d. with RTV 400 mg b.i.d..	Only approved for b.i.d. use. Must be used in combination with RTV. Causes GI disorders, hyperlipidemias.
	Lopinavir	LPV/r	133.3 mg LPV+ 33.3 mg RTV caps	3 caps b.i.d. or 6 caps q.d. (if treatment naive)	Can cause GI disorders, hyperlipidemia. Increase to 4 caps b.i.d. if combined with EFV or NVP.
	Atazanavir	ATV	100, 150, 200 mg caps	400 mg q.d.; 300 mg q.d. if boosted with 100 mg RTV	Causes elevated indirect bilirubin levels. Little lipid or GI effects. Must be ritonavir boosted when used with tenofovir.
	Fos-Amprrenavir	f-APV	700 mg tabs	1400 mg q.d. with 200 mg RTV or 700 mg b.i.d. with 100 mg RTV	Can cause rash, GI disorders, hyperlipidemia.
	Tipranavir	TPV	250 mg caps	500 mg q.d. with 200 mg RTV	Approved only in salvage therapy. Must be ritonavir boosted. Can cause hepatotoxicity GI disorders, hyperlipidemia. Not for use in patients with moderate/severe hepatic insufficiency.
	Darunavir	DRV	300 mg tabs	600 mg b.i.d. with 100 mg ritonavir boosting	Refunes potency in HIV moderately resistant to other drugs in PI class.
Fusion Inhibitor	Enfuvirtide	T20	Vial of 108 mg lyophilized powder reconstituted with 1.1 mL sterile water.	90 mg s.q. b.i.d.	Commonly causes injection site reactions.

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mutation that can lead to cross-resistance with some other drugs in this class. This mutation is rare if either a thymidine analog, or a potent 'cornerstone' drug is co-administered. Triple nucleoside regimens including tenofovir without either a thymidine NRTI or a potent third drug have led to a high viral breakthrough, frequently with the K65R mutation.^{46,47}

Abacavir (ABC) and Lamivudine (3TC)

The third NRTI co-formulation, also one pill, once daily, has had extensive clinical application.⁴⁸ Abacavir is a potent non-thymidine NRTI with no significant drug interactions. It, along with lamivudine, is well tolerated in long-term use. It, however, has an uncommon, but occasionally severe hypersensitivity reaction in early use characterized by fever, rash, malaise, and, in extreme cases where the drug is continued or reintroduced, circulatory collapse and death.^{49,50} The rate of this reaction may be reduced with genetic screening. Drug interactions with this combination are uncommon. Drug resistance patterns with abacavir are similar to tenofovir with a K65R mutation, but also seen is the L74V mutation.

Comments on Other NRTIs

Didanosine (ddI) is a drug used daily in an enteric coated formulation. It is well tolerated in the short term, although some note a mild gastrointestinal (GI) reaction. It has been associated with pancreatitis, usually in longer-term use, especially if combined with stavudine, a combination contraindicated in women and relatively contraindicated in all patients.⁵¹ Didanosine is often used with lamivudine, zidovudine or tenofovir. As tenofovir increases didanosine levels, dose adjustment is needed. An attenuated CD4 response to ARV therapy has been reported with tenofovir and didanosine, especially if the ddI dose is not appropriately reduced,^{52,53} and some trials have suggested a lower potency with the tenofovir combination when used with an NNRTI-based regimen.^{54,55}

Stavudine

This thymidine analog has been used extensively but is strongly associated with peripheral lipotrophy.⁵⁶ It can also cause peripheral neuropathy⁵⁷ when used with didanosine, pancreatitis and lactic acidosis.⁵¹ While well tolerated in short-term use, long-term toxicities limit its current application. Stavudine has also been used in generic formulations in resource constrained settings due to low cost. Even there, alternatives should be sought, if possible.

Cornerstone agents

Non-nucleoside RTIs

Efavirenz (EFV) Efavirenz is a potent, once daily NNRTI and the preferred 'third agent' in many initial ARV triple drug regimens.^{2,4} It is well tolerated in the long term. Short-term toxicity is usually temporary and does not require treatment interruption. Most common is a rash and/or central nervous system symptoms including vivid dreams.⁵⁸ The resistance pattern of efavirenz overlaps that of other drugs in this class. Even single mutations, especially K103N and Y181 C or I can lead to high level resistance. The long serum half-life of efavirenz, on the other hand, may allow durable activity and limited resistance selection even with compromised adherence.⁵⁹ One important aspect of efavirenz is its fetal toxicity.⁶⁰ Seen both in primate trials and in human use, efavirenz can cause CNS defects exposed in infants, especially in the first trimester. Efavirenz should be used extremely cautiously in women who may become pregnant while taking the drug. Other drugs should be used when possible. If efavirenz is used, women should be fully informed about the need for effective contraception.

Nevirapine Nevirapine is similar in many respects to efavirenz, but may be somewhat less potent. Its short-term toxicity also includes a rash^{61,62} but not the CNS side-effects of efavirenz. Nevirapine, however, has been associated with an uncommon but occasionally severe or even fatal hepatic hypersensitivity reaction.⁶³ This is more common in women and in those with more preserved CD4 cell counts. Its resistance overlaps that of efavirenz. Nevirapine has been widely used during pregnancy where it reduces HIV transmission to the infant.

Protease Inhibitors (PIs)

As a class, PIs have been associated with both short term and persisting GI distress and hyperlipidemia. One PI, indinavir, has a unique renal toxicity, as well as a retinoid-like constellation of cutaneous effects. One of the newer PIs, atazanavir, has no lipid effects, and less GI toxicity, but does commonly cause an elevated indirect hyperbilirubinemia, not infrequently with visible icterus or jaundice.

With the exception of nelfinavir, all PIs are pharmacologically boosted with the co-administration of low-dose ritonavir. This typically adds both potency and convenience, enabling less frequent administration and fewer pills per dose. As a class, PIs have a broad genetic resistance barrier. Each has a charac-

teristic set of induced mutations, described more fully in the chapter on ARV drug resistance.

Lopinavir (LPV)/Ritonavir (RTV) This co-formulated PI (the only one in this class) can be used once or twice daily.³⁰ It is potent but is associated with moderate GI complaints and can increase adverse lipid profiles.^{64,65} LPV/RTV has modest interactions with other ARV drugs, most notably with efavirenz. The potency and broad resistance barrier of this boosted PI and the unique convenience of the co-formulation have made it popular both as an initial 'cornerstone' agent and in salvage regimens. A newly released formulation may have less GI toxicity and does not require refrigeration.

Atazanavir (ATZ)/Ritonavir (RTV) Atazanavir is a newer PI and the first developed and approved for once daily administration.⁶⁶ Ritonavir boosting improves drug levels without apparently increased toxicity in shorter-term studies.⁶⁷ This combination is typically well tolerated with less GI and possibly by lipid effects than other PIs.⁶⁸ Indirect hyperbilirubinemia is common. While not a true hepatotoxicity, resulting sclera icterus or jaundice may be of concern to the treated patients who should be appropriately informed. Ritonavir boosted atazanavir has been most thoroughly tested in salvage regimens where it is approved in the USA. While widely used in initial therapy, studies for this indication are in progress. Atazanavir should not be used unboosted with tenofovir as its levels are reduced by that NRTI, and levels are reduced by the concurrent use of proton pump inhibitors.⁴⁵

Darunavir (DRV) Darunavir is a recently approved protease inhibitor. Its primary attraction is its potency against HIV with moderate resistance to other PI agents. It should be ritonavir boosted and its main use is in salvage regimens. It has typical PI side effects, including GI disturbance and hyperlipidemias.

Other Boosted PIs

In order of their development, indinavir (IDV), saquinavir (SQV) – in its two formulations as Inverse (INV) or Fortovase (FTV), and fos-amprenavir (fos-APV) are all boosted by low dose ritonavir. Though in somewhat less common current use than the other boosted PIs above, each is potent and can have a place in individualized ARV regimens. Indinavir is declining in use due to more common toxicities and dose inconvenience. Indinavir can cause hyperglycemia and uncommonly, renal disease.⁶⁹ More common side-effects include renal stones due

to precipitated excreted drug and retinoid-like cutaneous reactions.⁷⁰ Even boosted indinavir must be used twice daily, further limiting its use. Saquinavir (as the hard gel Inverse formulation⁷¹ – the soft gel having been removed from sales) and fos-amprenavir,^{72,73} by contrast are better tolerated, although like most other PIs can cause GI distress and hyperlipidemia. As with all boosted PIs, these agents have a broad genetic resistance barrier.

Nelfinavir (NFV) Unique among the PIs, nelfinavir is not ritonavir-boosted and is thus used alone. This, and the need for twice daily dosing, has limited its use except in ritonavir intolerant patients. It is a relatively potent drug, although probably less so than boosted PIs.³⁰ Nelfinavir commonly causes GI distress, especially diarrhea, and can raise serum lipid levels. It has been widely used during pregnancy where it is considered quite safe.⁷⁴

Fusion Inhibitors

Enfuvirtide (or T-20) is a polypeptide that blocks the entry of HIV into cells.²² It is given subcutaneously twice daily and is well tolerated apart from the need for injection and for nearly universal reactions at the injection site. When used along with other active drugs, enfuvirtide has been a potent antiviral drug.^{75,76} It is usually used against HIV with accumulated resistance to two or even all three of the other classes of antiretroviral medications.

Clinical Application of ARV Regimens

Successful management of HIV infection requires the prescription of a potent ARV drug combination at an appropriate point in the disease course. This regimen must be taken correctly and continuously during what is now a chronic and non-curable infection. Decisions are relatively straightforward with initial ARV therapy, but become much more complex later in the face of increasing drug resistance, seen over time in most patients, or with unexpected or severe side-effects or drug interactions.

ARV Regimen Design

The choice of a specific ARV regimen is an absolutely crucial one as a good choice, individualized for that person's needs and concerns can result in extremely gratifying disease recovery and durable benefit (Table 13.2). This choice should consider the patient's wishes for once or twice daily treatment, the need

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Table 13.2 Common antiretroviral regimens using FDC backbones

Regimen	Advantages	Disadvantages
[ZDV+3TC]+EFV		ZDV+3TC is b.i.d., EFV is q.d., two drugs with low resistance barrier.
[ZDV+3TC]+NVP	All b.i.d. after first 2 weeks	Two drugs with low resistance barrier, no q.d. option.
[ZDV+3TC]+[LPV/rvtv*]	All b.i.d. (although PI can be q.d.)	No q.d. option.
[ZDV+3TC]+SQV-hgc/rvtv	All b.i.d. (although PI can be q.d.)	No q.d. option.
[ZDV+3TC]+f-APV/rvtv	All b.i.d. (although PI can be q.d.)	No q.d. option.
[ZDV+3TC]+ATV/rvtv		ZDV+3TC is b.i.d., ATV/rvtv is q.d.
[ZDV+3TC]+IDV/rvtv	All b.i.d.	No q.d. option.
[ZDV+3TC]+NFV	All b.i.d.	No q.d. option.
[TDF+FTC]+EFV	All q.d. in two pills	Two drugs with low resistance barrier.
[TDF+FTC]+NVP		Two drugs with low resistance barrier, NVP usually b.i.d.
[TDF+FTC]+[LPV/rvtv]	Can be q.d.	
[TDF+FTC]+SQV-hgc/rvtv	Can be q.d.	
[TDF+FTC]+f-APV/rvtv	Can be q.d.	
[TDF+FTC]+ATV/rvtv	All q.d.	
[TDF+FTC]+IDV/rvtv		No q.d. option.
[TDF+FTC]+NFV		No q.d. option.
[ABC+3TC]+EFV	All q.d.	ABC and EFV can both cause rash, two drugs with low resistance barrier.
[ABC+3TC]+NVP		ABC and NVP can both cause rash, two drugs with low resistance barrier, NVP usually b.i.d.
[ABC+3TC]+[LPV/rvtv]	Can be q.d.	
[ABC+3TC]+SQV-hgc/rvtv	Can be q.d.	
[ABC+3TC]+f-APV/rvtv	Can be q.d.	ABC and f-APV can each cause rash.
[ABC+3TC]+ATV/rvtv	All q.d.	
[ABC+3TC]+IDV/rvtv		No q.d. option.
[ABC+3TC]+NFV		No q.d. option.
[ZDV+3TC+ABC]	All one pill b.i.d.	Less potent than regimens with NNRTI or PI component.

for other medications that might cause adverse interactions, and other health conditions, such as hyperlipidemia that may increase long term complications with certain drugs. Also, the patient's concern for specific side-effects should be elicited. For example, some patients are less willing to tolerate ongoing diarrhea, even if mild, which can complicate some ARV drugs. Some patients find the vivid dreams, sometimes associated with efavirenz, disturbing, while others do not.

Ideally, all ARV agents can be used simultaneously without complicating restrictions on food or

fluid intake. All possible drug interactions, both within the ARV regimen and with any other prescribed or non-prescribed drugs, must also be considered and, when possible, avoided. The presence of pre-existing genetic ARV resistance mutations should be tested. While not yet in common use, host genomic testing might identify variations in drug toxicity or metabolism, enabling even more rational regimen design. Certain HLA types, for example, are associated with a higher risk for abacavir hypersensitivity⁷⁷ and, if detected, may lead to the choice of alternative agents.

Optimal Timing of Initial ARV Therapy

ARV therapy of very recently acquired HIV infection is of uncertain benefit, and the appropriate subject of ongoing clinical trials.^{78,79} Chronic HIV infection – generally defined as beginning about 12 months after exposure – should be treated before the onset of opportunistic infections or malignancies. Where available, treatment is guided by CD4+ T-lymphocyte counts and, to a lesser degree, plasma viral loads. Specific drug regimens are selected based on existing ARV drug resistance and by the patient's specific circumstances. Absent resource constraints, US and most European guidelines suggest ARV initiation after the CD4 cell count falls below 350 cells/mm³ but before it falls below 200/mm³.^{2,4} When resources are very limited, ARV is recommended at the onset of clinical disease or when the CD4 count falls below 200/mm³.⁸⁰ Immunologic and clinical recovery is expected even when ARV use is delayed until late disease stages, but immune restoration may be less robust in those cases.^{81,82} Experimental data suggest even earlier ARV initiation – before the CD4 count falls to 350/mm³ for example – may prove superior, but this is still the subject of ongoing clinical investigation.⁸³ As a treatment strategy, such very early treatment may allow later prolonged periods of intentional drug interruption to limit drug exposure before reinitiation prompted by a decline in CD4 cell counts, but this remains controversial given recent failures of trials using this approach.⁸⁴

Before ARV is first prescribed, co-incident illness should be considered as it may affect ARV choice. In advanced stage HIV disease, opportunistic infections or cancers may require immediate management. Whether ARV drugs should be used while acute opportunistic infections are being controlled, or deferred for some time is unknown. Patients may also have infections related to their HIV exposure history such as sexually transmitted infections or those related to parental or maternal exposure including hepatitis viruses B or C. Pregnancy should also be considered as it can affect the choice of ARV drugs. Most notably, efavirenz should be avoided in pregnancy.⁶⁰ Chronic health problems that may be exacerbated during ARV therapy such as hyperlipidemia or hyperglycemia should be diagnosed and appropriately managed. Also, a thorough medication history is required as ARV drugs may lead to adverse interactions. The drug history should include non-prescription and illicit agents, and herbal remedies. Proton-pump inhibitors and H2 blockers, in common over-the-counter use, should be specifically assessed as they can decrease the absorption of ARV drugs –

notably atazanavir.⁸⁵ Finally, underlying factors that might affect drug absorption or metabolism should be assessed at baseline, especially renal function. Guidelines for ARV use in the setting of chronic kidney disease are currently being published.⁸⁶

The patient should be fully informed before ARV drugs are first prescribed. Patient counseling should include information on potential drug side-effects, the importance of excellent and continuous medication adherence, and the need for on-going safe transmission behavior. The patient initiating ARV should have access to sources knowledgeable in ARV use should questions or concerns arise.

Baseline laboratory testing should ideally include CD4 cell counts and plasma viral load and, increasingly, drug resistance genotyping. In resource constrained settings, laboratory tests may not be available, and clinical recovery used to guide treatment decisions. CD4 cell counts are fundamentally important, however, and techniques to reduce their cost will hopefully increase their availability.⁸⁷

There are no widely accepted standards for laboratory monitoring of ARV therapy. Most would repeat the viral load within several weeks of treatment initiation to both assess and support prescription adherence. At the same visit, side-effects can be discussed as they contribute to longer-term non-adherence and may be reduced by regimen alteration or the prescription of other drugs.

The goal of initial ARV therapy, reducing plasma viral load below assay detection limits, is commonly achieved within 12 weeks, but may require 24 weeks of treatment, especially if the pre-treatment baseline viral load was extremely high.⁸⁸ Non-adherence should be suspected if the plasma viral load fails to fall quickly, or if it plateaus above detection levels. Prolonged viremia in the face of ARV exposure will result in drug resistance selection, limiting treatment benefits.

Laboratory testing shortly after ARV initiation is also useful to detect drug toxicity. Early adverse effects of ARV drugs include hepatotoxicity, dyslipidemias, hyperbilirubinemia and anemia. There are no specific guidelines for toxicity monitoring which should be driven by the specific agents used and host susceptibility, and, of course, any interval clinical signs or symptoms.

The frequency of clinical and laboratory monitoring varies after plasma HIV titers fall below detection limits. Many practitioners ask patients to be seen every three to four months if all is going well. With very stable patients, this interval can gradually be extended, but usually to no longer than every 6 months. Each visit should address potential drug

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toxicity and problems specific to HIV disease. Medication adherence should be assessed and reinforced at each visit as should safe HIV transmission risk behavior.

Experimental Strategies in Initial ARV Therapy

Patients on successful ARV regimens with high CD4 cell counts have often temporarily discontinued therapy. The CD4 cell count usually falls very slowly in such cases, especially if the prior CD4 nadir was not very depressed.⁸⁹ Those observations have led to prospective clinical trials in which ARV treatment is stopped until the CD4 count falls to a pre-specified level. In the Italian BASTA trial, treatment was stopped at a CD4 cell count above 800/mm³ and was reinstated when the CD4 count fell below 400/mm³,⁹⁰ while the SMART study (recently halted due to inferior outcome with treatment interruption) aimed to keep the CD4 count between 250 mm³ and 350/mm³. Current trials are exploring this concept more fully. If positive, such studies might lead to early ARV use while the CD4 cell count is still in a higher range. This strategy might avoid any irreversible immune damage associated with a CD4 cell count fall to low levels. If the off-treatment intervals were substantially longer than the on-treatment periods, the overall cost of treatment might also be reduced. Such a strategy would require care in drug discontinuation to prevent resistance selection. If CD4 testing was available, this strategy could find application in some resource constrained settings.

Induction-maintenance

Interest continues in the concept of beginning ARV therapy with more complex and potentially toxic regimens, followed by a shift to a simpler combination.^{91,92} This might be especially attractive in those at higher treatment failure risk such as with a very low baseline CD4 cell count or high levels of viremia. It might also allow the shorter-term use of drugs, such as stavudine that cause severe toxicity with prolonged use, and it is possible that less potent combinations such as those with only three nucleosides may maintain adequate viremia suppression once 'full' suppression is achieved by a more aggressive combination. This remains unproven and an appropriate subject for clinical trials.

Viral Failure

Current ARV regimens are sufficiently potent to suppress viremia in almost all patients.¹ If this does not happen, several causes should be examined. First, the patient may have been infected at baseline with HIV already harboring drug resistance. This can be due to non-disclosed prior treatment or to having acquired ARV-resistant HIV. Resistance as a cause of treatment failure can be reduced with baseline resistance testing, if available.

Another consideration is poor drug exposure due to malabsorption or drug interaction. The former is rare and drug interactions can be avoided by a careful baseline drug history, again including non-prescription products. Of non-ARV drugs, interactions threatening ARV response are most common with gastric acid blockers, especially the potent proton pump inhibitors⁸⁵ and with antituberculosis therapy, where rifomycin interactions with protease inhibitors are common.⁹³

The most common cause of initial ARV failure is poor medication adherence.^{36,94} Non-adherence can be intermittent or nearly continuous. It can involve the entire regimen or only selected agents. Non-adherence can be seen with the first doses prescribed or can occur at any later point, even after prolonged periods of excellent compliance. It may reflect a lack of appropriate baseline counseling, the onset of drug side-effects, or interval substance or alcohol misuse. It, finally, may represent 'treatment fatigue.'

ARV drug resistance often accompanies virologic failure and every case of insufficient suppression or rebound viremia should prompt genotype testing if possible. Virologic failure of the first or even second regimen should prompt an immediate reattempt to again suppress viremia below detection limits. As dictated by circumstances, this may involve adherence support or a change of one or more drugs to reduce side-effects or to correct for resistance mutations. Resuppression in early failure is typically straightforward if non-adherence is the cause and can be corrected.

Virologic failure in the face of multiple resistance mutations is much more difficult to reverse. Non-nucleoside reverse transcriptase resistance mutations affect the entire drug class. Certain mutations in the nucleoside and protease classes also cause extensive cross-resistance. Each case of such 'late failure' is so unique in terms of prior drugs used, toxicity experienced and drug resistance patterns seen that broad generalizations are inescapable (and thus of limited practical value) in suggesting man-

agement strategies. One key issue is whether full viremia suppression is still a reasonable goal in the specific patient's care. If so, a new drug regimen designed to resuppress viremia should be initiated. If not, continued therapy is usually preferred to full discontinuation. Brief discontinuation to allow wild type HIV outgrowth followed by reinitiation – often termed strategic or structured treatment interruption – is of unproven value.^{95,96} Certain resistance mutations – especially those in the nucleoside reverse transcriptase class may decrease HIV fitness, as estimated by *in vitro* replication capacity.⁹⁷ Regimen selection aimed at limiting HIV fitness is increasingly popular – and understandable, given the limited options – but of unproven value.^{98,99} (See Ch. 15 for a fuller discussion of this biology.)

Specific Management Approaches in Virologic Failure

Non-adherence to Prescribed Regimen

A crucial question is whether the patient simply stopped all medications or stopped only selected drugs. Also key, is whether non-adherence was intermittent or continuous. Was non-adherence triggered by side-effects or inconvenience of the prescribed regimen? Finally and critically, did non-adherence result in resistance selection? In all these cases, the need for rigorous adherence should be stressed along with practical advice on how this can be achieved. Absent toxicity or resistance, the ARV regimen originally prescribed can be continued if adherence can be re-established, and if significant resistance mutations have not yet been selected.

Toxicity to Selected Drugs

ARV side-effects range from minor inconveniences to life-threatening in severity (see Ch. 17 for an expanded discussion of ARV toxicity). Some are transient, others continue over time. Some can be ameliorated with other medications while others are not treatable. Serious side-effects may require permanent avoidance of the offending drug. Hypersensitivity reactions to abacavir or idiosyncratic nevirapine hepatotoxicity are examples of this extreme. On the other hand, some side-effects are temporary and the drug can be continued. Examples here are early CNS side-effects with efavirenz or most rashes with efavirenz or nevirapine. Yet another general toxicity type is that which can be controlled with additional medications if the offending ARV cannot be easily substituted. Zidovudine associated

anemia can be reversed at least partially by recombinant erythropoietin and hyperlipidemias can be controlled, although often only partially, with diet, exercise or statins. In these cases, the ARV causing the side-effect can either be continued, along with the additional medication, or can be replaced with one not having this toxicity. Finally, some ARV side-effects are chronic and essentially irreversible. Stavudine-associated peripheral lipoatrophy and diarrhea second to nelfinavir continue as long as these agents are prescribed. In these situations, the drug causing the side-effect can either be continued or not, depending on severity and patient tolerance. With lipoatrophy, little reversal is seen even with prolonged discontinuation, while nelfinavir-associated diarrhea promptly resolves when the drug is stopped.

An important aspect of ARV toxicity is the effect of 'minor' but chronic treatment side-effects. Over time, these can lead to non-adherence. Patients should be asked specifically about the impact of chronic low-level gastrointestinal or CNS toxicity. If present, changing to other drugs should be considered.

Topics in 'Late' Salvage ARV Therapy

Adding a New Drug to a 'Failing' Regimen

The approval of a new drug adds hope for viremia control in those with ongoing viremia and multiple drug resistance. Adding a single new drug, whether of a new and non-cross resistant class as with enfuvirtide, or with less cross resistance like tipranavir is, itself, of limited value. Unless a new drug can be used with at least one, or preferably two, other active agents, its introduction is rapidly followed by drug resistance selection. Guidelines, therefore increasingly suggest the earlier use of such new agents to improve the hope of re-suppression of viremia with more durable clinical benefits.²

'Partial Treatment'

If viremia suppression below detection limits is an unrealistic goal, ongoing ARV use may yet be of clinical utility. The resistance mutations of certain drugs seem to impair HIV 'fitness' and thus *in vivo* virulence, and some drugs may have partial residual antiviral activity even with what appears to be high phenotypic resistance. Discontinuing all ARV therapy in advanced stage HIV disease is often followed by rapid CD4 cell count declines. In contrast,

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relative CD4 cell count stability, has been seen when some drugs are continued.¹⁰⁰ Typically, this continued therapy includes, at a minimum, two NRTIs and often a PI. In these cases, drugs to be continued should be well tolerated and ones which maintain an impaired HIV replication capacity. It should be stressed, however, that this area is the subject of ongoing research and is of unproven efficacy.

ARV Treatment Approaches in Resource-constrained Settings

There is no difference in the goal of ARV therapy in resource-limited settings, but the access to drugs and monitoring tests may necessitate very different choices. Otherwise, preferred agents may not be available and the low cost of certain generic fixed-dose combinations may require their use even if they contain more toxic ARV drugs. In many countries, important drugs like protease inhibitors are too expensive for common use while stavudine is used because of its low cost even though its associated lipotrophy is well known. Drugs like ritonavir that require refrigerated storage may be impractical where electrical power and appliances are limited. Common co-infections, especially tuberculosis, also pose a problem in ARV therapy. Drugs needed for tuberculosis therapy, rifampicins particularly, interact with protease inhibitors.

Laboratory tests may also be unavailable in many settings. ARV therapy can be effectively initiated on the basis of clinical condition but is substantially aided by CD4 test results. HIV viral load testing is much less important in initiating ARV therapy, but is of clear utility in managing subsequent treatment failure.

WHO Guidelines suggest ARV initiation when the CD4 falls below 200/mm³ or in symptomatic persons.⁸⁰ Clinical or CD4 improvements are then followed as evidence of treatment benefit and ARV therapy is continued until either shows progressive disease. The choice of ARV regimens in many countries is severely limited, often consisting primarily of generic fixed-dose combinations. Secondary regimens are even more constrained. Initial regimens often are non-nucleoside based and protease inhibitors may not be available for salvage. CD4 testing is more widely available than HIV viral load testing and resistance tests are generally unavailable. Each element of this discussion, however, is changing rapidly as more international funding for HIV care is reaching many countries most affected by the HIV epidemic.

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