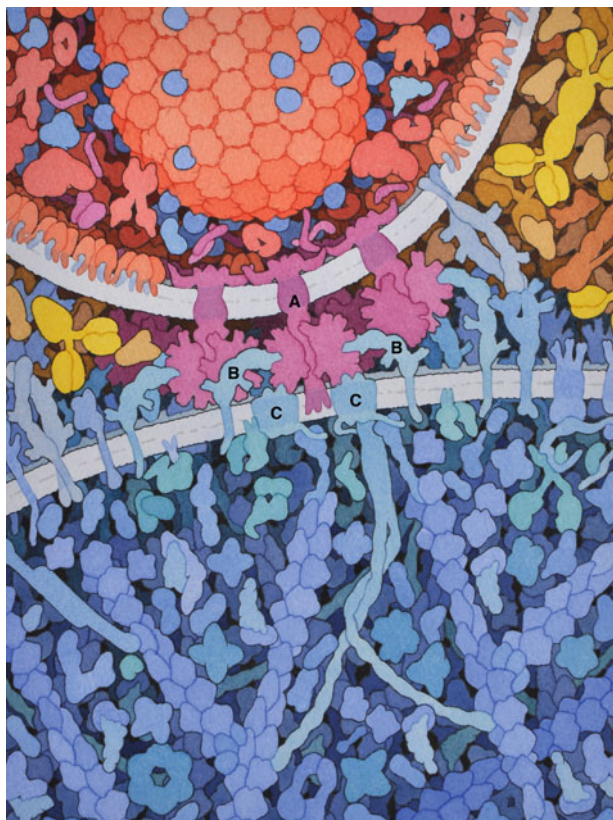# HIV Therapy—The State of ART

David Looney, Ariel Ma and Scott Johns

HIV Attachment. In this cross section, HIV is shown at the top and a target cell is shown at the bottom in blues. HIV envelope protein (*A*) has bound to the receptor CD4 (*B*) and then to coreceptor CCR5 (*C*), causing a change in conformation that inserts fusion peptides into the cellular membrane

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Abstract Antiretroviral therapy changed the face of HIV/AIDS from that of soon and certain death to that of a chronic disease in the years following introduction of highly active antiretroviral therapy in 1995–1996 (initially termed HAART, but now most often abbreviated to ART since not all combinations of regimens are equally active). Since then, many new agents have been developed and introduced in response to problems of resistance, toxicity, and tolerability, and great advances have been achieved in accessibility of HIV drugs in resource-poor global regions. Potential challenges that providers of HIV therapy will face in the coming decade include continuing problems with resistance, especially where access to drugs is inconsistent, determining how best to combine new and existing agents, defining the role of preventive treatment (pre-exposure prophylaxis or PrEP), and evaluating the potential of strategies for cure in some populations.

Abbreviations

HAART	Highly active antiretroviral therapy
ART	Antiretroviral therapy
HIV, HIV-1	Human immunodeficiency virus, human immunodeficiency virus type 1
AIDS	Acquired immune deficiency syndrome
PrEP	Pre-exposure prophylaxis
AZT	Zidovudine
ddI	Didanosine
ddC	Zalcitidine
d4T	Stavudine
3TC	Lamivudine
FTC	Emtricitabine
ABC	Abacavir
TDF	Tenofovir disoproxil fumarate
RT	Reverse transcriptase
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
NVP	Nevirapine
EFV	Efavirenz
ETV	Etravirine
DLV	Delavirdine
RPV	Rilpivirine
SQV	Saquinavir
IDV	Indinavir
NFV	Nelfinavir
FPV	Fosamprenavir
LPV	Lopinavir
RTV/r	Ritonavir
TPV	Tipranavir
ATV	Atazanavir

DRV	Darunavir
T20	Enfurvirtide
RAL	Raltegravir
ETG	Elvitegravir
DTG	Dolutegravir
MVC	Maraviroc
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
TP	Triphosphate
NS5A	Non-structural protein 5A of hepatitis C virus
Kd	Kilodalton
PI	Protease inhibitor
INSTI	Integrase strand transfer inhibitor
CSF	Cerebrospinal fluid
CYP3A	Cytochrome P450 isoform protein 3A
HBV	Hepatitis B virus
HCV	Hepatitis C virus
DHHS	Department of health and human services
IC50	Inhibitory concentration 50 %
PCR	Polymerase chain reaction
SREBP-1	Sterol regulator element-binding protein 1
PPAR-gamma	Peroxisome proliferator-activated receptor gamma
OAT, OATP	Organic anion transporter
gUGT	Glucuronosyltransferase
CNS	Central nervous system
MDR1	Multidrug resistance transporter 1
HSCT	Hematopoetic stem cell transplant
CCR5	CC Chemokine receptor 5 gene
ANRS	Agence Nationale de Recherche sur le Sida
VISCONTI	Virological and immunological studies in controllers after treatment interruption
CD3	Cluster of differentiation surface marker 3
CD4	Cluster of differentiation surface marker 4
HDAC	Histodeacytelase inhibitor
CRISPR	Clustered regularly interspaced short palindromic repeat protein
Cas-9	CRISPR-associated protein 9
Fem-PrEP	Women's preventative treatment study
VOICE	Vaginal and oral interventions to control the epidemic
MSM	Men who have sex with men
US	United States
IVDU	Intravenous drug users
CDC	Centers for Disease Control

NIH	National Institutes of Health
DAIDS	Division of AIDS
NIAID	National Institute of Allergy and Infectious Disease
NIMH	National Institute of Mental Health
NIDA	National Institute of Drug Abuse
NICHD	National Institute of Child Health and Human Development
NHLBI	National Heart Lung and Blood Institute
NIGMS	National Institute of General Medical Sciences
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIA	National Institute on Aging
PPI	Proton pump inhibitor
ADH	Alcohol dehydrogenase
OCT2	Organic cation transporter 2
MATE1	Multidrug and toxin extrusion protein 1
UGT1A	Uracil diphosphate glucuronosyltransferase 1 protein family
CYPnLn, nLn	Cytochrome protein isoforms of P-450, e.g., CYP1A2 or 1A2, CYP1A6, or 1A6.

Contents

1 Introduction

The progress in chemotherapy of human immunodeficiency virus infection (HIV) ranks as one of the great success stories of infectious disease. Advances in treatment over the past 25 years have accompanied milestones in our understanding of the virology and immunopathogenesis of disease, reflect triumphs of rational drug design, and encompass a plethora of findings from careful and comprehensive clinical research. Where it is available, highly active antiretroviral therapy (ART) has dramatically lowered mortality not only from HIV disease, but from all causes, especially cardiovascular disease, as well. While the convenience, efficacy, and toxicity of antiviral therapy have improved remarkably from the era of early treatment, when lactic acidosis, lipodystrophy, and severe neuropathy were accepted as regrettable trade-offs of survival, acquired antiviral resistance persists,

increasing primary HIV antiviral drug resistance has emerged. Furthermore, the development of resistance in areas where drug access is limited present a growing problem. In addition, the cross-resistance of many drugs within classes, adverse pharmacologic interactions between antiretroviral agents and other antiretrovirals as well as drugs commonly used for other medical conditions can still quickly make acceptable choices for regimens difficult.

This chapter aims to present a brief look at the current armamentarium, give some insight into current clinical problems and treatment strategies, and highlight areas where advances in activity and pharmacologic profile are needed.

2 The Medicine Cabinet—Current Antiretroviral Drugs

Background and Introduction: The number of pharmaceuticals approved for the treatment of AIDS and HIV infection in the United States grew from one (zidovudine, AZT) in 1987 to include thirty individual agents and eight fixed-dose combination tablets by 2014 (some no longer available, some additional combination agents are available abroad—see Fig. 1). Many approved medications were discovered via high-throughput screening efforts, while others were developed principally through rational drug design based on structural biology. The latter approach has proven particularly effective in developing second- and third-generation drugs in several different classes, which can be used against virus resistant to earlier, similar drugs.

Approved antiretroviral drugs for HIV still target only four viral and one host protein (see Fig. 1): Nucleoside (zidovudine—AZT, didanosine—ddI, zalcitabine—ddC is no longer available, stavudine—D4T, lamivudine—3TC, and abacavir—ABC) and nucleotide (tenofovir, TDF) reverse transcriptase (RT) inhibitors act both as competitive inhibitors and chain terminators within the active site of the HIV viral RNA-dependent DNA polymerase, blocking efficient synthesis of proviral DNA. Non-nucleoside reverse transcriptase inhibitors (nevirapine—NVP, efavirenz—EFV, etravirine—ETV, rilpivirine—RPV) bind to site(s) outside the catalytic active site producing structural changes in the enzyme that render it incapable of normal function. Approved protease inhibitors (saquinavir—SQV, indinavir—IDV, nelfinavir—NFV, fosamprenavir—FPV, lopinavir—LPV, tipranavir—TPV, atazanavir—ATV, and darunavir—DRV) are all derivatives of structural analogs of the natural enzyme cleavage site and function as potent competitive inhibitors. Enfuvirtide (Fuzeon^{TM}, T20), an injectable peptide drug, binds to the transmembrane portion of the HIV envelope protein (TM, gp41), stabilizing the conformation, preventing infection by blocking a structural change needed for entry of virus into CD4+ cells. Integrase inhibitors (raltegravir—RAL, elvitegravir—ETG, and dolutegravir—DTG) block the strand transfer function of HIV-1 integrase, preventing integration of the reversed-transcribed provirus into host genomic DNA, resulting in abortive, if any, viral transcription. A drug targeting one of the two most
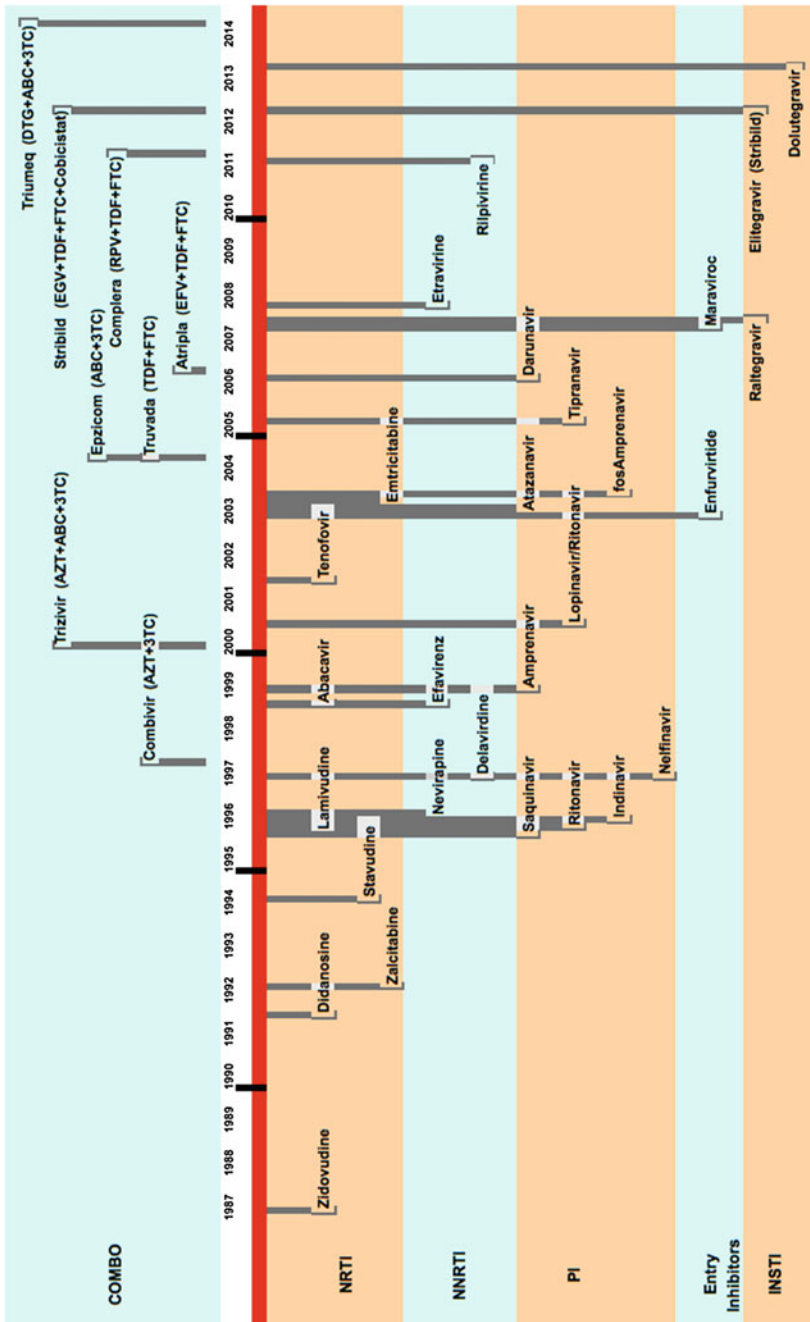
Fig. 1 Time line for approval of antivirals in the United States. Time from left to right from 1997 to 2014 (*red bar*). Combination tablets including single-tablet combination regimens are shown at the top, cyan background. NRTI, NNRTI, PI, entry inhibitors, and INSTIs are shown below the time line in alternating beige and cyan background. *Vertical lines* for each drug represent quarter of year of approval [data from 17, archival guidelines, and multiple other sources]

common cell-surface coreceptor molecules used by HIV (CCR5), maraviroc (MVC), is also in clinical use.

Each class of antiretroviral drug is very briefly reviewed below, mechanism(s) of action explained in more detail, and some prominent pharmacokinetic characteristics and adverse effects are noted.

Currently Approved Reverse Transcriptase Inhibitors: These include seven nucleoside/nucleotide analogs (NRTIs) and five non-nucleoside inhibitors (NNR-TIs) of HIV-1 RT (see Fig. 1 and following). Three agents in this class were introduced but are no longer available and/or recommended due to toxicity (ddC, zalcitabine, Hivid[TM]) and pharmacokinetics (delavirdine, DLV, Rescriptor[TM]—no longer marketed by Agouron but revived by ViiV, and non-enteric coated ddI—Videx).

Nucleoside Reverse Transcriptase Inhibitors (*NRTIs*). Stemming from work in the 1960s and 1970s, modified dideoxynucleotides similar in structure to NRTIs were studied as DNA chain terminators for use in cancer therapy (Toji and Cohen 1969; Yatchoan and Broder 1987), including screening for antineoplastic activity. AZT, the first approved antiretroviral agent, is still in use and serves as an example. The structure of AZT differs from deoxythymidine in the presence of a 3′ azido rather than a 3′ hydroxy group. Activity requires intracellular phosphorylation at the 5′ position by thymidine kinase to form AZT-5′-monophosphate, phosphorylation to AZT-5′-diphosphate by thymidylate kinase, and conversion to AZT-5′-triphosphate (AZT-TP) by nucleoside diphosphate kinase. AZT-TP is a substrate for viral RT (and to a lesser degree host enzymes), but the azido group at the 3′ position of AZT does not allow further 5′–3′ phosphodiester linkages to form. AZT competes with thymidine for access to the active site of reverse transcriptase and prematurely terminates chain elongation once incorporated into the DNA strand (Yatchoan and Broder 1987; Furman et al. 1986; St Clair et al. 1987). While AZT and other NRTI agents have a greater affinity for reverse transcriptase than cellular DNA polymerases alpha, beta, or epsilon, mitochondrial DNA polymerase is susceptible to varying degrees, and incorporation of AZT into germ-line DNA and vertical transmission of modified DNA has been noted (see toxicity) (Yatchoan and Broder 1987; St Clair et al. 1987).

Each NRTI is an analog of a DNA nucleoside or nucleotide, including structural analogs of thymidine (zidovudine—AZT, stavudine—D4T), cytosine (lamivudine—3TC, emtricitabine—FTC), guanine (abacavir—ABC), and adenosine (didansosine—DDI, tenofovir—TDF). Tenofovir is the only currently approved nucleotide (monophosphate) NRTI.

The NRTI antiretrovirals have only few metabolic interactions of importance. Though abacavir is a substrate for both alcohol dehydrogenase and uracil transferase enzymes, no dosage adjustment is required. Lamivudine, emtricitabine, and tenofovir require dosage reduction in renal insufficiency. Tenofovir also reduces exposure to atazanavir by mechanism(s) that remain unelucidated, and tenofovir also has an important interaction with ledipasvir, a new hepatitis C NS5A inhibitor (Rockstroh 2015).

Non-nucleoside Reverse Transcriptase Inhibitors (*NNRTIs*). Approved NNRTI antiretrovirals in the United States include nevirapine (NVP), delavirdine (DLV), efavirenz (EFV), etravirine (ETV), and rilpivirine (RPV). Unlike NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs) are not structural homologues of DNA nucleotides, rather binding reverse transcriptase at an allosteric site ~ 10 Å distant from the catalytic site. Binding induces conformational changes, which alters substrate binding and affects translocation of double-stranded DNA. NNRTIs are non-competitive inhibitors of the reverse transcriptase enzyme (Mao et al. 2000; Crauwels et al. 2012; Kohlstaedt et al. 1992; Pollard et al. 1998; Smerdon et al. 1994). Currently, there are five NNRTIs available in the United States for the treatment of HIV infection (Fig. 1). Just as for the NRTI class of antiretroviral agents, the NNRTIs have also been associated with significant toxicity. As a class, all agents share the potential for causing cutaneous reactions, sometimes severe ones.

Metabolism of all NNRTI drugs processed largely through CYP3A4, and all but rilpivirine induces their own metabolism (Crauwels et al. 2012). Efavirenz and nevirapine are metabolized and induced by CYP2B6, and etravirine is metabolized and inhibited by CYP2C9 and CYP2C19 (see Table 1).

Entry (attachment and fusion) Inhibitors. The first entry and only approved fusion inhibitor is Fuzeon (Loutfy et al. 2007), approved in 2003 for use in the United States. A number of additional entry inhibitors have been evaluated in clinical and preclinical trials, including enhanced peptide-based fusion inhibitors (T-1249), and antagonists of envelope binding to the CXCR4 co-receptor (most are toxic), the CD4 receptor, and cell-surface galactosyl ceramide. Monoclonal antibodies that interfere with entry have also been explored. However, the only other entry inhibitor approved at the time of this writing is maraviroc®, a small molecule that targets the CCR5 coreceptor molecule. Maraviroc (MVC) (Dorr et al. 2005) is metabolized primarily by CYP3A4, is also a substrate for the P-glycoprotein efflux pump, and requires dosage adjustment with protease inhibitors and/or NNRTI drugs given in combination.

Protease Inhibitors: HIV protease is a virally encoded aspartyl protease that prefers phenylalanine–proline or tyrosine–proline containing substrates. Two 65-Kd pol precursor polyproteins must first interact to form an active dimer which then self-cleaves and acts to cleave other individual proteins (e.g., matrix and capsid proteins, reverse transcriptase and integrase proteins) from gag and pol polyprotein precursors. The mature protease has two identical 99 amino acid monomers arranged in a donut-like homodimer. Protease inhibitors are competitive inhibitors of catalyzed cleavage that have high affinity for the preferred peptide substrate cleavage site. Protease inhibitors (PIs) do not block infection by viral particles produced in the absence of PI, but in the presence of PI only non-infectious and immature (the core never condenses as the capsid protein is never cleaved) viral particles are produced (Merrett 1990).

The crystal structure of the HIV protease was first determined by X-ray diffraction in 1988 (Merrett 1990). Protease inhibitors are essential analogs of phenylalanine-proline that competitively inhibits the enzyme because of chemical

Table 1 Metabolic pathways important to drug–drug interactions. [See (Kim 2003; Mathias 2010)]

Enzyme/Pathway	PPI	Renal	ADH	UGT1Ax	P-gp	BCR P	OCT2/MATE1	OATP 1B1/1B3	1A2	1A6	2B6	2C8	2C9	2C19	2D6	3A4
NRTI																
3TC		++														
ABC			X	X												
FTC		++														
TDF		++														
ZDV		++														
NNRTI																
EFV											X←	→	→			X←
ETV					→								X↓	X↓		X←
NVP											X←				x	X←
RPV	+															X
PI																
ATV	+			→								→				X↓
DRV															→	→
LPV																X
Entry																
Maraviroc					X											X
Fuzeon																
INSTI																
RAL				X												
ETG				X									←			X
DTG				X			→									X
Booster																
RTV				←	X↓				←		←		X↓	←	↓↓↓	X↓↓↑
Cobicistat					→	→		→							X↓	X↓

Symbol Key:

x	Minor Substrate	↓	Potent Inhibitor
X	Major Substrate	↑	Potent Inducer
→	Inhibitor	+	Requires stomach acid for absorption
←	Inducer	++	Requires renal dose adjustment

affinity for the active site. Drug resistance is primarily mediated by mutations resulting in subsequent amino acid substitutions both near and distant (producing conformational changes) to the active site, which affects drug-binding affinity. In addition, compensatory mutations in the gag polyprotein which introduce more favored or altered cleavage may allow proteases otherwise impaired by changes needed to escape PI inhibition to function more effectively.

In vitro activity of early peptide analogs was documented as early as 1990, and by 1993 candidate drugs were entering human trials, and the first protease inhibitor, saquinavir (SQV, Invirase) was approved for use in the United States, in 1995, followed by ritonavir (RTV) and indinavir (IDV) in the next year, and by nelfinavir (NFV), amprenavir (APV), lopinavir/ritonavir combination (LPV/r) atazanavir (ATV), fosamprenavir (FPV), tipranavir (TPV), and darunavir (DRV) over the next decade (see Fig. 1).

Pharmacokinetics of Protease Inhibitors. Each agent is available exclusively in oral dosage form though absorption may be limited. One strategy included use of presolubilized soft gel capsules for absorption (RTV, APV, LPV/RTV, Fortovase soft gel capsules) and addition of agents such as vitamin E (APV). Many of these have been supplanted (LPV/RTV available in tablet and solution, RTV available in capsule and tablet, ATV, TPV, SQV, and IDV capsules) and/or withdrawn from the market (unmodified Amprenavir, Fortovase). Distribution throughout the body varies, but while CSF penetration tends to be low (CSF usually averages ~ 4 % of serum concentration), this is still within the active range. All share metabolism via the P-450 mixed function oxidase system, including primarily CYP3A (see Table 2). Various protease inhibitors also inhibit and/or induce cytochrome oxidases, conjugation, and membrane transport proteins, leading to many drug

Table 2 Pharmacological characteristics of protease inhibitors

Drug	Absorption (%)	Half-life (h)	Protein binding (%)	Isoenzyme substrate	Isoenzyme inhibitor
Saquinavir	4[+]	13	97	CYP3A4	CYP3A4
Ritonavir	60	3–5	98	CYP2D6, CYP3A4	CYP2D6. CYP3A4, CYP2C9, CYP2C19
Indinavir	30	1.8	60	CYP3A4	CYP3A4
Nelfinavir	20–80	3.5–5	99	CYP3A4, 2CP2C19	CYP3A4
Lopinavir/ ritonavir	NA[a]	5–6	99	CYP3A4, CYP2D6	CYP2D6. CYP3A4, CYP2C9, CYP2C19
Atazanavir	NA[a]	6.5	86	CYP3A4	CYP3A4, UGT1A1, CYP1A2,CYP2C9
Darunavir	NA[a]	15[a]	95	CYP3A4	CYP3A4, CYP2D6
Fosamprenavir	63	7.7	90	CY2C9, CYP2D6	CYP3A4
Tipranavir	NA[a]	6	99	CYP3A4	CYP2D6

[a]Used exclusively with ritonavir, bioavailability and half-life reflect this

interactions with other medications. These can be troublesome, but are also sometimes useful pharmacokinetic interactions, as between ritonavir (and now cobicistat), which is co-administered to prolong the half-life and area under the curve (AUC—i.e., cumulative drug exposure, a product of concentration over time) of all currently used protease inhibitors except nelfinavir (see Table 2) (Fellay et al. 2002; Kim 2003).

Integrase Inhibitors: HIV-1 integrase is a multifunctional enzyme that catalyzes the insertion of reverse transcribed viral DNA into the host genome. Integrase removes the two terminal 3′ nucleotides from the 5′ U3 and 3′ U5 LTR ends of linear viral DNA (3′–5′ exonuclease), makes a 5 bp staggered cut in host double-stranded DNA (endonuclease), and mediates strand transfer between the processed viral and cleaved genomic DNA (ligase) (Craigie 2001). Theoretically, disruption of any step in the integration process should efficiently inhibit viral replication, but all currently approved medications in this class are integrase strand transfer inhibitors (INSTIs), including raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG). While initially often used in patients resistant to other classes of antiretrovirals, INSTIs are increasingly being used in first-line regimens given their potency and favorable side-effect profiles. In addition, for reasons that remain incompletely understood, INSTIs suppress HIV replication in the blood more quickly than any other class of antiretrovirals.

3 Current Treatment—Who, What, When, Why, and How

Who to treat and why: Over the last twenty-five years, the goals of antiretroviral therapy have evolved from the desperate attempt to prolong the duration and quality of life in critically ill AIDS patients with limited tools (Fischl et al. 1987; Cooper et al. 1993). Currently, there are multiple objectives (Department of Health and Human Services 2014) influencing treatment of HIV-infected individuals: (1) To achieve durable suppression and immune reconstitution, avoiding "AIDS-related" infections and other complications, treating HIV as a chronic disease that must be controlled, not unlike diabetes or hypertension; (2) To reduce all-cause morbidity and mortality, most notably by reducing inflammation and thereby improving cardiovascular and neoplastic co-morbidity (Kuller et al. 2008; Sandler et al. 2011; Duprez et al. 2012; Borges et al. 2013; Smith 2010; Sabin et al. 2008; Bedimo et al. 2009; Shiels et al. 2011; Worm et al. 2013); (3) To prevent transmission of HIV, "test to treat" strategies (Nachega et al. 2014; Kretzschmar et al. 2013; Kulkarni et al. 2013; DeGruttola et al. 2010) can ultimately lower the prevalence of disease; (4) There is evidence that HIV treatment is helpful in reducing the otherwise accelerated progression of hepatitis C infection in co-infected individuals and also may aid HCV treatment; and finally (5) To effectively cure HIV infection, while not yet possible, early treatment can reduce viral set point and "total body burden," which may be critical factors in the success of new modalities which emerge to

produce potential eradication of infection (Department of Health and Human Services 2014).

These goals are reflected in the changes in the Department of Health and Human Services (DHHS) guidelines over the years (Table 3). From 1998 to 2003, treatment was largely recommended to prevent complications arising directly from HIV disease. Only in 2004 had sufficient evidence accumulated that treatment of individuals before critical immunological depletion (i.e., before CD4 of <350/mm^3) with high viral loads (>100,000 copies/ml) was recommended for consideration for treatment. From 2007 to 2011, guidelines urged consideration of therapy in asymptomatic individuals with higher CD4 cells, but with delayed therapy acceptable in those with >350 or >500 T cells. Since 2012, antiretroviral therapy (ART) has been recommended in all individuals (see Table 3) (Department of Health and Human Services 2014).

With What & How—General Principals of Therapy: The DHHS guidelines on antiretroviral are properly based on validated clinical trial data and experience, but that does not obviate the potential usefulness of models that might predict superior activity and/or better combinations for clinical exploration beyond what can be deduced by pharmacokinetic data and in vitro antiviral activity studies. Historically, there have been interesting and at times contrasting theories and interpretations. For example, AZT was initially given every 4 h based on plasma levels, but studies of intracellular concentrations later showed this to be unnecessary, and it is now often given only twice daily (Fletcher et al. 1998). Similarly, in the early 1990s "convergent therapy" with three nucleotides targeting the reverse transcriptase was predicted on the basis of in vitro modeling to create a genetic barrier to which the virus would be unable to surmount with resistance mutations (Chow et al. 1993), then quickly derided and the paradigm that multiple enzymes would needed to be targeted when ABC+AZT+3TC (triple NRTI) failed in trials (Emini et al. 1993), and revised again to reflect two mechanisms of action (though perhaps on the same enzyme) when Atripla (NNRTI + two NRTI) became a successful mainstay of therapy.

From 1995 until the introduction of the integrase strand inhibitors, only protease inhibitors and non-nucleoside reverse transcriptase inhibitors were felt to be potent enough to form the backbone of successful antiretroviral regimens, but these two differed very widely in barrier to resistance, and the reason and nature of the greater potency remained unexplained, particularly as the in vitro IC$_{50}$ values did not differentiate PIs and NNRTIs from NRTIs. From 2011 to 2014, a "critical subset" model, postulating that multiple copies of a drug target must remain active to allow replication to progress, was found to correlate with steeper dose-response curves for NNRTI and PI antiretrovirals (Shen et al. 2011; Jilek et al. 2012; Laskey and Siliciano 2014). While both NRTIs and INSTIs exhibit flatter curves, the integrase inhibitors, most potent of all the antiretrovirals, are not subject to this model (i.e., inhibition of even one site prevents replication), at least possibly explaining the lower effectiveness of NRTIs compared to these other drugs.

Some hard and soft "don'ts." Some clinicians feel uncomfortable using an NNRTI regimen (especially rilpivirine) in those with very high viral loads

Table 3 DHHS treatment recommendations over time

		When to Start												
Year	1998	1999	2000	2001	2002	2003	2004	2005-2006	2007	2008	2009	2010-2011	2012-2013	2014
All	AIDS, symptomatic HIV, CD4<200/mm³*	AIDS, symptomatic HIV, CD4<200/mm³*	AIDS, symptomatic HIV, CD4<200/mm³*	AIDS, symptomatic HIV, CD4<200/mm³*	AIDS, symptomatic HIV, CD4<200/mm³*	AIDS, symptomatic HIV, CD4<200/mm³*	AIDS, symptomatic HIV, CD4<200/mm³*	AIDS, symptomatic HIV, CD4<200/mm³*	AIDS, symptomatic HIV, CD4<350/mm³*	AIDS, symptomatic HIV, CD4<350/mm³*	AIDS, symptomatic HIV, CD4<350/mm³*	AIDS, symptomatic HIV, CD4<350/mm³*	All HIV-infected	All HIV-infected
Special Populations									Pregnancy, HBV Coinfection, HIV Nephropathy	Pregnancy, HBV Coinfection, HIV Nephropathy	Pregnancy, HBV Coinfection, HIV Nephropathy	Pregnancy, HBV Coinfection, HIV Nephropathy, Serodiscordant	Pregnancy, HBV Coinfection, HIV Nephropathy, Serodiscordant, Prevent Transmission	Pregnancy, HBV Coinfection, HIV Nephropathy, HCV Infection, Prevent Transmission
Consider or Offer Therapy	CD4<500, HIV VL>10-20,000	CD4<500, HIV VL>10-20,000	CD4<500, HIV VL>10-20,000	No Recommendation	Before CD4 declines below 200	Before CD4 declines below 200	CD4 201-350 OR CD4>350 AND VL>100K	CD4 201-350 OR CD4>350 AND VL>100K	CD4>350	CD4>350	Treat: CD4>500 / Defer: CD4>500	Treat: CD4>500 / Defer: CD4>500		

		What to Use												
	1998	1999	2000	2001	2002	2003	2004	2005-2006	2007	2008	2009	2010-2011	2012-2013	2014
NRTI Pairs	d4T+3TC d4T+ddI ZDV+3TC ZDV+ddC ZDV+ddI	3TC+ddI d4T+3TC d4T+ddI ZDV+3TC ZDV+ddC ZDV+ddI	d4T+3TC d4T+ddI ZDV+3TC ZDV+ddI	d4T+3TC d4T+ddI ZDV+3TC ZDV+ddI	3TC+ddI d4T+3TC d4T+ddI ZDV+3TC ZDV+ddI	d4T+3TC TDF+3TC ZDV+3TC	d4T+3TC TDF+3TC ZDV+3TC	TDF+3TC TDF+FTC ZDV+3TC ZDV+FTC	TDF/FTC ZDV/3TC	TDF/FTC	TDF/FTC	TDF/FTC	TDF/FTC	ABC/3TC TDF/FTC
NNRTIs		EFV	EFV	EFV	EFV	EFV	EFV	EFV	EFV	EFV	EFV	EFV	EFV	EFV/TDF/FTC VL<100K only; EFV+2NRTI RPV/TDF/FTC
PI	IDV NFV RTV SQV RTV+SQV	IDV NFV RTV SQV RTV+SQV	IDV NFV RTV+SQV	IDV IDV/r NFV LPV/RTV RTV+SQV	IDV IDV/r NFV LPV/RTV RTV+SQV	LPV/RTV	LPV/RTV	LPV/RTV	ATV/r fosAPV/r LPV/RTV	ATV/r DRV/r fosAPV/r LPV/RTV	ATV/r DRV/r	ATV/r DRV/r	ATV/r DRV/r	ATV/r+TDF/FTC DRV/r+TDF/FTC VL<100K only; ATV/r+ABC/3TC
INSTI											RAL	RAL	RAL	RAL+TDF/FTC ET/Gcobi/TDF/FTC DTG+TDF/FTC DTG+ABC/3TC

(>100,000 copies/ml) or where concern for resistance is high. (Rimsky et al. 2012; Pozniak et al. 2010). The concomitant use of tenofovir and abacavir should be avoided, as the risk of virological failure is significant (Gilliam et al. 2007). Most clinicians would not add or change a single agent in a regimen with overt viro- logical failure (HIV RNA rising and/or >5000 copies/ml), but addition of single agents as "consolidation therapy" for patients achieving a significant antiviral response falling short of complete suppression is not uncommon, but should be guided by resistance testing where feasible. Avoidance of agents with additive or synergistic toxicities (e.g., d4T and ddI), adverse intracellular interactions (e.g., AZT and d4T or 3TC and ddC), and adverse pharmacokinetics (e.g., saquinavir and efavirenz) is another general principal of therapy.

Treatment of antiretroviral-experienced individuals who have undergone failures of one or more regimens must be guided by genotypic and/or phenotypic resistance testing (see "Technologies for Monitoring and Guiding Treatment," following) assessment of adherence (e.g., review of prescription refill data), careful consid- eration of absorption limiting drug-drug or drug/disease interactions, possibly approached by therapeutic drug monitoring, review of prior treatment ("archived" resistant variants may escape detection by conventional resistance testing), avail- ability of agents of classes not previously included in the patient's treatment history (e.g., INSTIs, NNRTIs, Fuzeon), and the patient's potential for tolerating additional or different drugs (Montaner et al. 2001; Youle et al. 2002; Lalezari et al. 2003; Lazzarin et al. 2003).

Historical Notes. The manner in which we treat patients infected with HIV has undergone remarkable changes. Zidovudine monotherapy was the only option available from 1997 to 1991 (see Fig. 1). By the time didanosine was approved in 1991, many individuals who had experienced a transient response from zidovudine were simply switched to didanosine, and later to zalcitabine (1992) or stavudine (1994) as these new drugs became available. Sequential monotherapy was associ- ated with greater survival than continued zidovudine or cessation of therapy (Graham et al. 1996), but HIV variants with multiple drug resistance mutations predictably accumulated (Iversen et al. 1996).

Combination therapy produced greater and more sustained response (Iversen et al. 1996; Meng et al. 1992; Collier et al. 1993; Schooley et al. 1996; Gulick et al. 1997; Johnson and Sax 2014) and has improved with the introduction of less toxic and better tolerated therapies. With the introduction of protease inhibitors saquin- avir, ritonavir, and indinavir in combination with NRTIs in 1995 and 1996 (Gulick et al. 1997), highly active antiretroviral therapy (HAART) produced profound and durable suppression of HIV in the plasma, with marked reductions in mortality, becoming the standard of care by 1998 (Table 3). The subsequent introduction of additional abacavir and tenofovir, additional protease inhibitors and NNRTIs (NVP, EFV, ETV, RPV) have led to regimens with increased efficacy and reduced toxicity (Fig. 1). Subsequent second-generation PIs (TPV, DRV) and introduction of INSTIs (RAL, ELG, DTG) allowed formulation of regimens that were more potent, and both less toxic for initial therapy while also being active against many resistant strains (Johnson and Sax 2014).

Technologies for Monitoring and Guiding Treatment. Assays to quantify HIV replication (Ho et al. 1995; Saag et al. 1996) established the relationship between HIV RNA viral load and the risk of disease progression and death (Mellors et al. 1997). Elaboration of the kinetics of HIV replication (Perelson et al. 1996) facilitated more clinical trials by allowing rapid comparison of regimens using "surrogate" (i.e., non-clinical) endpoints, as well as expediting early identification of successful and failing therapy in clinical practice. Most recently droplet digital PCR (Strain et al. 2013) has provided the ability to quantify very low viral loads consistently, allowing an approach for a clinical definition of strategies for cure (see following).

HIV resistance testing (Tang and Shafer 2012) has also undergone considerable evolution in sophistication over the years. Routine use of genotyping using conventional capillary sequencing of the reverse transcriptase and protease in genomic HIV RNA present in plasma virions followed viral load monitoring by only a few years, allowing prediction of prevalent populations of virus bearing resistance mutations (Shafer 2002). Phenotyping has involved cloning portions or all of the pol genes derived by RT-PCR from plasma virus into a reference reporter clone expressing luciferase, transfecting recombinant virus and measuring virus infection in the presence of increasing concentrations of drug (Richman 2000), which is very analogous to conventional antimicrobial sensitivity testing. The availability of large databanks of virus for which both phenotypic and genotypic resistance data allowed the introduction of "virtual phenotyping," to more accurately predict resistance from sequence data (Larder et al. 2000; Hertogs et al. 2000). A number of allele-specific PCR-based assays capable of detecting minor populations of resistant virus (esp. NNRTIs) have become available, and some have found their way into potential point of care devices (Paredes et al. 2007; Palmer et al. 2006; Hunt et al. 2014). Finally, next-generation sequencing of the entire polymerase or even the complete viral genome is beginning to be used to better predict the success of possible therapeutic regimens (Hunt et al. 2014; Garcia-Diaz et al. 2014; Simen et al. 2014). Clinical studies have indicated better short- and long-term outcomes in clinical settings when clinicians are provided with the results of testing (Cingolani et al. 2002; Clevenbergh et al. 2000; Baxter et al. 2000; Tural et al. 2002), especially when expert advice in interpretation is also provided (Baxter et al. 2000; Tural et al. 2002). Current guidelines suggest that resistance testing should be obtained in cases of virological failure, incomplete suppression, prior to initiation of antiretroviral therapy, and in acute HIV infection, due to increasing transmission of drug-resistant strains during primary infection (Little et al. 2002), which is especially relevant in resource-poor settings where monitoring and availability of antiretrovirals may be intermittent (Hamers et al. 2013).

Barriers to Treatment: Include identifying those with HIV infection, providing access to treatment, and maintaining patients in care on therapy, termed the continuum of HIV care, as well as problems of adherence, toxicity, and resistance.

Access and the Continuum of HIV care. Clearly access is an overriding while clearly surmountable hurdle for treatment. It is estimated that 1.3 million individuals in the United States are infected with HIV of whom only 400,000 are in care

and only 200,000 are suppressed on treatment (CDC 2011). Worldwide, nearly 35 million individuals are estimated to be infected with HIV, with 2 million newly infected in 2013, while only 12.9 million have access to antiretrovirals, and a smaller number still are suppressed (World Health Organization 2014). Progress, however, has been made: Nearly 67 % of HIV+ pregnant women receive pro-phylactic treatment, and over 2 million people were started on antiretrovirals worldwide (World Health Organization 2014).

Adherence and Tolerability. As noted above, many earlier drugs were quite toxic, frequently producing "minor" issues of nausea, diarrhea, rash, and other symptoms. In addition, the pill burden of earlier antiretroviral regimens was stag-gering—a patient requiring amprenavir, didanosine, and lamivudine in the late nineties could look forward to eighteen tablets and capsules of antiretrovirals a day at staggered times four times daily. With the introduction of Epzicom (ABC+3TC) and Truvada (TDF+FTC) in 2004 and the routine use of boosted protease inhibitors such as ATV/r and later DRV/r, regimens containing 2–4 doses once daily became common. Finally, with the introduction of Atripla (EFV+TDF+FTC) in 2006, and subsequently Complera (RPV+TDF+FTC), Stribild (EGV+Cobi+TDF+FTC), and most recently Triumeq (DTG+ABC+3TC), a single-pill, highly potent, fixed-dose regimens have assumed the preferred position in recommended therapy and become goals of future drug development (see Fig. 1). New combination tablets that will likely be available by the time this review appears include atazanavir/cobicistat, darunavir/cobicistat, elvitegravir/cobicistat, and elvitegravir/cobicistat/emtricita-bine/tenofovir alafenamide (United States Food and Drug Administration 2014).

Adherence is also a critical factor in the success or failure of antiretroviral therapy with a direct relationship to pharmacokinetics of available drugs. Studies indicate that lower than 95 % adherence—one missed dose in a twice daily regimen once every ten days—may lower the success rate by up to 20 % (Paterson et al. 2000; Knobel et al. 1998). Promotion of adherence by reducing pill burden, decreasing frequency of administration, establishing a rapport with the patient, and involving the patient in treatment decisions, proper pharmacy instruction and monitoring, and provision of pill boxes or other organizers, electronic reminders, or phone calls have all been explored (Chesney 2003).

Toxicity and Metabolic Effects. The newer antiretroviral regimens avoid many but not all of these problems, but the legacy of prior use of more toxic antiretro-virals and combinations remains in the clinic today. Mitochondrial effects have been minimized by largely restricting NRTI use to tenofovir, abacavir, lamivudine, and emtricitabine. These are the least potent inhibitors of mitochondrial DNA-dependent DNA polymerase gamma. Prolonged treatment otherwise results in depletion of mitochondrial DNA and loss of mitochondria, leading in the extreme to lactic acidosis (Feng et al. 2001; Arenas-Pinto et al. 2003), pancreatitis, hepatitis, and muscle weakness (Boubaker et al. 2001; Coghlan et al. 2001). Individual "bad" NRTIs manifested different patterns of toxicity, AZT characteristically causing myopathy (Arnaudo et al. 1991), while ddI (particularly when used with d4T) was associated with pancreatitis (Moore et al. 2001; Scribner et al. 2000). The same "D" drugs (d4T, ddI) were strongly implicated in avascular necrosis of the femoral

heads, of femur and tibia in the knee, and even of the shoulder girdle, although this may also be related to steroid exposure during treatment of pneumocystis pneumonia, alcoholism, smoking, and other risk factors (Brown and Crane 2001; Valencia et al. 2003) encountered more frequently in the HIV-infected population.

Glucose intolerance, hypertriglyceridemia, and hypercholesterolemia (Carr et al. 1881, 1998; Caron et al. 2001) can be induced by protease inhibitors, more so with first-generation PIs (e.g., indinavir) as well as the NRTIs 3TC and FTC (Dressman et al. 2003; Lenhard et al. 2000). These changes may be mediated by changes in nuclear localization of the sterol regulatory element-binding protein-1 (SREBP-1) and changes in expression of peroxisome proliferator-activated receptor gamma (PPAR-gamma) and the insulin receptor (Caron et al. 2001). A variety of studies have reported that lipodystrophy (fat redistribution) and accelerated atherosclerotic disease occurring in individuals treated with HAART have been associated with total time on HAART (Caron et al. 2001; Dressman et al. 2003; Lenhard et al. 2000; Carr 2000; Bozzette et al. 2003; Friiis-Møller et al. 2003; Bogner et al. 2001; Mallon et al. 2003; Blanco et al. 2003; Seminari et al. 2002; Joly et al. 2002; Worm et al. 2002).

In addition to the previously mentioned association between abacavir hypersensitivity and host genotype (Mallal et al. 2002), other associations between response to antivirals and genetic background have been noted, including significant variation in serum levels of efavirenz and nelfinavir obtained during therapy in individuals with polymorphisms in the multidrug resistance transporter 1 gene (MDR1), organic anion transporters (OAT), P-450 alleles, and uracil gUGT (Fellay et al. 2002). Different alleles of the MDR1/P-glycoprotein efflux system may also affect CNS levels of antiretroviral drugs (Kim 2003). Polymorphisms uncommon in the Caucasian and European populations but common in individuals of African descent strongly affect efavirenz metabolism, leading to increased toxicity in susceptible individuals.

Resistance. While the medicine cabinet seems replete with choices, a little resistance can go a long way in limiting effective therapy, often requiring more toxic and less tolerable combinations to be effective. Drug resistance can be either transmitted with a founding virus or acquired, as the result of treatment to prior regimens. As noted above, the latter was common during the introduction of HAART in the mid- and late 1990s, as a large proportion of the population had acquired NRTI resistance. This led to acquisition of resistance to early protease inhibitor regimens, and often to NNRTI resistance after introduction of first-generation NNRTIs. Often the only choice was to wait, to maintain patients on failing regimens, until the time that two or more agents with full activity became available. Later drugs in most antiretroviral classes were designed to both increase activity against viruses resistant to earlier members and increase the genetic barrier to resistance (see Fig. 2—genetic barrier to resistance). Among NRTIs, tenofovir appears less susceptible, likely because of decreased replication fitness in mutants harboring the K65R mutation. Similarly, among NNRTIs, etravirine provides some rescue of K103N positive strains resistant to nevirapine and efavirenz (though Y181C, frequent in recipients of nevirapine, remains significant). To some extent tipranavir, and to a greater extent

Fig. 2 Genotypic barrier to resistance in antiretroviral drugs. *Vertically*, INSTI, NRTI, NNRTI, and PI classes are shown from *top* to *bottom* in alternating *light gray* and *light blue* backgrounds (see text for drug abbreviations:. *Horizontal* grouping of drugs by number of mutations needed to render the antiretroviral ineffective are very approximate, as mutations at single positions that have higher replication cost (K65R, multi-NTRI substitution mutations) can still inactivate some drugs (e.g., tenofovir, loprinavir, and darunavir) shown further to the right in the figure. Data extrapolated from multiple sources (Emini et al. 1993; Tang and Shafer 2012; Shafer 2002; Richman 2000; Larder et al. 2000; Hertogs et al. 2000; Paredes et al. 1955; Palmer et al. 2006; Hunt et al. 2014; Garcia-Diaz et al. 2014; Simen et al. 2014; Wensing et al. 2014)

darunavir, are examples of protease inhibitors developed to be active against strains resistant to many or all other PIs. While INSTIs were only introduced in 2007 and generally require several mutations to completely abolish antiviral activity, the newest, dolutegravir, also retain activity against some raltegravir-resistant strains (Tang and Shafer 2012; Shafer 2002; Richman 2000; Larder et al. 2000; Hertogs et al. 2000; Wensing et al. 2014; Castagna et al. 2014).

Drug–Drug interactions. Some antiretrovirals should never be used together due to metabolic antagonism (e.g., zidovudine and stavudine), and many cannot be used together with other antiretrovirals or with other medications a patient may be taking due to non-HIV-related medical conditions. Some antivirals require acid conditions for absorption (e.g., ATV, RPV) and should not be used with caution or avoided in patients on proton pump inhibitors or H2 antihistamines for acid-peptic disease. Others require dosage adjustment in patients with reduced renal function (e.g., 3TC, FTC, and TDF). Analysis of the patterns of efflux pumps (MDRs, MRDPs, OATs, others), elimination (e.g., UGT1A1 glucuronidation), metabolism, inhibition, and induction (principally microsomal enzymes) sometimes predict favorable and unfavorable interactions (see Table 1, "Metabolic pathways important to drug-drug interactions"), but may also fail to predict significant interactions (e.g., tenofovir reduction of atazanavir concentrations) and may suggest avoidance of combinations where only minimal changes occur (e.g., nevirapine and azole antifungals) when drug levels are measured. There appears to be no substitute for empiric determination.

4 Toward a Cure, (dys)Functional, or Otherwise

The philosophy of "treat early, treat hard" as a strategy for cure must be understood only in light of estimates that ranged as low as 4 years for the virus to disappear in the body of infected individuals. As data accumulated on rate of decay of proviral HIV DNA in resting memory T cells (Ho et al. 1995; Saag et al. 1996; Mellors et al. 1997; Perelson et al. 1996; Strain et al. 2013; Chun et al. 1995), the best estimates for the half-lives of viral reservoirs increased to the point that it was uncertain that any decay was taking place at all. Current data suggest that complete suppression of virus for a lifetime might not achieve cure (Strain et al. 2003) by antiviral treatment alone.

However anecdotal and some systematic study data suggest that cure of HIV may be possible, at least in some certain situations. A great deal of popular media coverage has been devoted to "The Berlin Patient" who received an hematopoietic stem cell transplant (HSCT) for acute myelogenous leukemia from a non-related donor homozygous for the CCR5Δ32 mutation (Hutter et al. 2009), conferring resistance to R5 tropic HIV-1 [note this same description has been used for an earlier elite controller (Jessen et al. 2014)]. This patient has remained free of replicating virus (but not completely free of fragments of proviral RNA as detectable by droplet digital PCR) (Yukl et al. 2013). Two additional patients who were heterozygous for CCR5Δ32 underwent HSCT using matched donors who were wild-type CCR5+ ("The Boston Patients") in 2010 (Henrich et al. 2013). While viral DNA disappeared in transplanted subjects while on therapy, both experienced viral rebound 12–32 weeks after stopping ART (Henrich et al. 2014).

Other examples have stirred hope that cure of HIV-1 infection might be effected by treated very early with potent therapy, after which ART could be withdrawn, with persistent suppression of viral replication. The so-called Mississippi Baby, who was treated beginning 30 h after birth with ART for 18 months, which was then withdrawn, with undetectable viremia for years (Persaud et al. 2013). The "Mississippi Baby's" mother was a long-term non-progressor, suggesting potential genetic factors. However, this infant relapsed with the mother's virus after two years off of therapy (Rainwater-Lovett et al. 2015).

A longer, more heterogeneous, and less well-controlled literature has reported long-term control after early treatment followed by treatment cessation, most recently exemplified by 14 individuals treated within 2 months of acquiring HIV infection in the ANRS VISCONTI trial (Sáez-Cirión et al. 2013) who have had extended periods of low-level viremia off ART for 48–115 months. Importantly, the majority of these individuals do have detectable viremia and cannot be considered "cured" in a virological sense. Whether this simply reflects a tiny minority with outlying delayed stochastic reactivation, compared to prompt reactivation of replication in 3–8 weeks in most who stop ART (Deeks et al. 2005), or reflects some as yet undescribed genetic or functional advantage is unclear.

Regardless of inspiration, there has been a growing emphasis on the attempted eradication of HIV by activating HIV replication in the face of ongoing ART, a

strategy termed "kick and kill." Initial efforts to do this with agents such as anti-CD3 and interleukin-2 (Prins et al. 1999) showed substantial toxicity. The most clinically advanced current studies have employed better tolerated histone deacetylase inhibitors (HDACs) such as vorinostat (Archin et al. 2012, 2014) and romidepsin (Wei et al. 2014) while continuing ART. These and other attempted interventions have not as yet shown much of an effect on overall HIV viral burden (Rasmussen et al. 2013), but other agents and/or more complicated or esoteric strategies (e.g., autologous stem transplantation with engineered CRISPR/Cas-9 CCR5 knockout or other perturbations, additional pharmacologic agents) are actively being explored (Rasmussen et al. 2013).

5 Preventative Treatment

While there have been some discrepant results in the use of both topical and oral tenofovir for the prevention of HIV infection [e.g., the FemPrEP (Van Damme et al. 2012) and VOICE trials (Peterson et al. 2007)], most studies have found that taken consistently, tenofovir, or especially tenofovir + emtricitabine (Truvada) can effectively reduce acquisition of HIV by up to 90 % in a variety of populations, including men who have sex with men (Grant et al. 2010; Grohskopf et al. 2013), heterosexuals (Baeten et al. 2012; Thigpen et al. 2012), and IV drug users (Choopanya et al. 2013). The studies that failed to show protective effects generally were plagued by low adherence as ascertained by report and/or pill count (FemPrEP) or with low levels of detectable drug despite good reported adherence (VOICE trial, 80 %+ by report or pill count but with only 30 % detectable drug on pharmacologic monitoring). Aside from these failures, results seem remarkably consistent across widely varying populations and geographic regions: (1) The PrEx trial showed 46 % reduction in MSM overall with 92 % in those with levels of TDF/FTC detectable in the blood (based in South America (Peterson et al. 2007), and in the US MSM trial none of 6 participants who seroconverted had yet received drug, (2) In the PartnersPrep Trial, overall estimates of efficacy were 67 % for tenofovir alone and 75 % for Truvada (Grohskopf et al. 2013), and the TDF2 trial showed an overall efficacy of 62 % in reduction of infection (Baeten et al. 2012). (3) In IVDU in Bangkok, Thailand, an overall reduction of infection of 48 % was achieved, increasing to 74 % in those displaying detectable tenofovir in their blood upon testing (Choopanya et al. 2013).

While trials are still ongoing including investigation of alternative strategies other than daily, continuous drug treatment, the evidence is sufficiently compelling that the CDC has issued guidelines for PrEP in high-risk individuals, including suggesting monitoring practices (US Public Health Service 2014). Resistance, while infrequent, has been described to result from preventative treatment (Peterson et al. 2007; Grant et al. 2010; Grohskopf et al. 2013) and remains a concern to clinicians and for public health as PrEP treatment becomes more widespread.

6 Concluding Remarks

Optimal drug treatment of HIV infection is a rapidly moving, continuously improving target (Department of Health and Human Services 2014). There are considerable incentives to develop new agents with entirely different mechanisms of action as well as improved generations of current drugs that display more favorable pharmacokinetics, lower toxicity profiles, and have activity against strains resistant to currently available agents. Exploration of strategies to possibly permanent (or at least durable) cure of some patient populations is in progress. New technologies, including drug monitoring, genetic testing, and improved resistance testing, may also expedite achievement of therapeutic goals. The expansion of HIV treatment to new populations presents unique challenges, and the use of antiretrovirals for preventative treatment, while it may save millions of lives, may also risk making resistance to the most commonly used agents more widespread.

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