Current Topics in Microbiology and Immunology

Bruce E. Torbett
David S. Goodsell
Douglas D. Richman *Editors*

The Future of HIV-1 Therapeutics

Resistance Is Futile?

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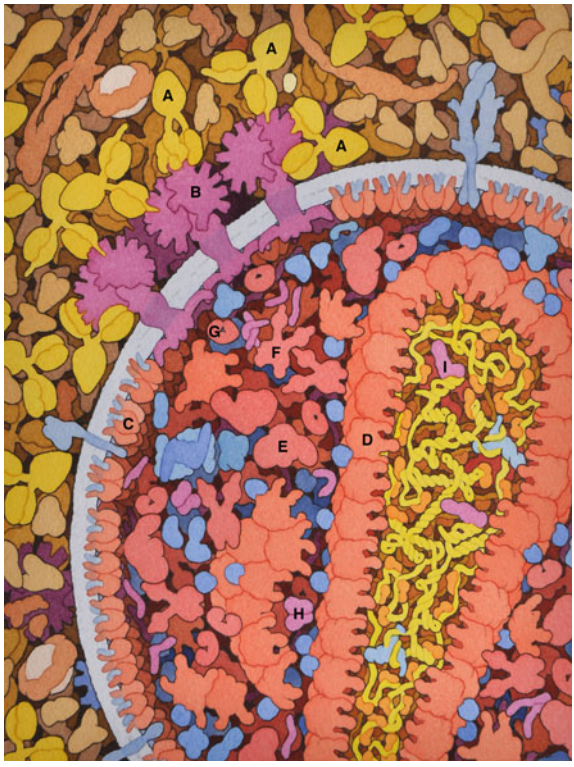
Preface



HIV and Antibodies. In this cross-section, HIV is shown at lower right, with viral proteins in red and magenta, and viral RNA in yellow. Blood plasma is shown at the top and left side. Several broadly neutralizing antibodies (*A*), are binding to HIV envelope glycoprotein (*B*). Other viral proteins include matrix (*C*), capsid (*D*), reverse transcriptase (*E*), integrase (*F*), protease (*G*), Vif (*H*), and Tat (*I*)

The development of antiretroviral drugs and the implementation of combination antiretroviral therapy for the treatment of human immunodeficiency virus type 1 (HIV-1) ranks as one of the great success stories of clinical management of an infectious disease. Treatment with highly active retroviral therapy has altered the disease course in millions of individuals from a death due to acquired immunodeficiency syndrome (AIDS) to one of managed care. Since the epidemic was first reported in 1981, approximately 78 million people worldwide have been infected with HIV-1, with an estimated 39 million deaths occuring.[1] Increased access to antiretroviral therapy, combined with a declining incidence of HIV-1 infection, has resulted globally in a significant drop in the number of adults and children dying from HIV-related causes. WHO has estimated that antiretroviral therapy programs have averted ~7.6 million deaths between 1995–2013.[2]

The number of drugs approved for antiretroviral use since the introduction of zidovudine (AZT) in 1987 has blossomed to include 30 individual drugs and at least 8 fixed-dose combination antiretroviral therapies (See Chapter "HIV Therapy—The State of ART"). The approved drugs target just four viral proteins, protease, integrase, reverse transcriptase, and gp41, and the host chemokine receptor, CCR5, used by the virus to enter cells. The use of combination antiretroviral therapy with drugs targeting distinct viral pathways reduces the chance of selecting for mutations that confer resistance to any single treatment. Current combination therapies can control HIV-1 for extended periods, allowing life expectances to approach that of uninfected individuals. However, these therapies will not lead to viral eradication, as the virus can be maintained in reservoirs that are not susceptible to current treatment. Combination therapies are expensive and compliance can be difficult; viral drug resistance does occur and is higher in resource-limited areas. Furthermore, drug-resistant viruses can be transmitted creating further complications for treatment and reducing the chances of effective treatment. Therefore, new antiretrovirals are needed that target different viral components as well as protease, integrase, or reverse transcriptase in a novel fashion.

The development of novel chemistries and methods for small molecule screening has coincided with an increased knowledge of HIV-1 biology and viral protein structures, prompting a renewed effort to identify the next generation of compounds that target old and new viral targets. In this edition of Current Topics in Immunology and Microbiology, each author has taken the challenge to discuss what may be new on the horizon for antiretrovirals; this has resulted in a review series that is both timely and informative. A common theme that emerges throughout Chapters "Nucleocapsid Protein: A Desirable Target for Future Therapies Against HIV-1" to "The Triple Threat of HIV-1 Protease Inhibitors" is that by focusing on the disruption of multiple discrete viral pathways, we can provide more effective therapy that is less prone to the development of antiretroviral resistance. The understanding of how viral components interact with each other, host cell

[1] http://www.who.int/gho/hiv/epidemic_status/deaths_text/en

[2] http://www.who.int/gho/hiv/epidemic_status/deaths_text/en

components, and small molecule inhibitors, strongly relies on structure-based modeling. The computational challenges of structure-based modeling for providing a molecular understanding of viral components interacting with inhibitors, as well as insights into antiretroviral resistance, is presented in Chapter "Computational Challenges of Structure-Based Approaches Applied to HIV". Lastly, for each chapter an illustration is provided for the viral component discussed in an attempt to integrate what is known from structural biology, electron microscopy, and biophysical studies with the goal of providing a view of the macromolecular structure of HIV in its cellular environment. To produce each illustration required an in-depth analysis of the available literature, which is discussed in Chapter "Illustrations of the HIV Life Cycle". Together, the assembled reviews in this edition of Current Topics in Microbiology and Immunology chart the horizon of HIV-1 antiretroviral research. We would like to thank the authors for their contributions of timely and insightful reviews and patience throughout the writing of this issue. Special thanks to Andrea Schlitzberger, Ph.D., for her editorial insights and patience.

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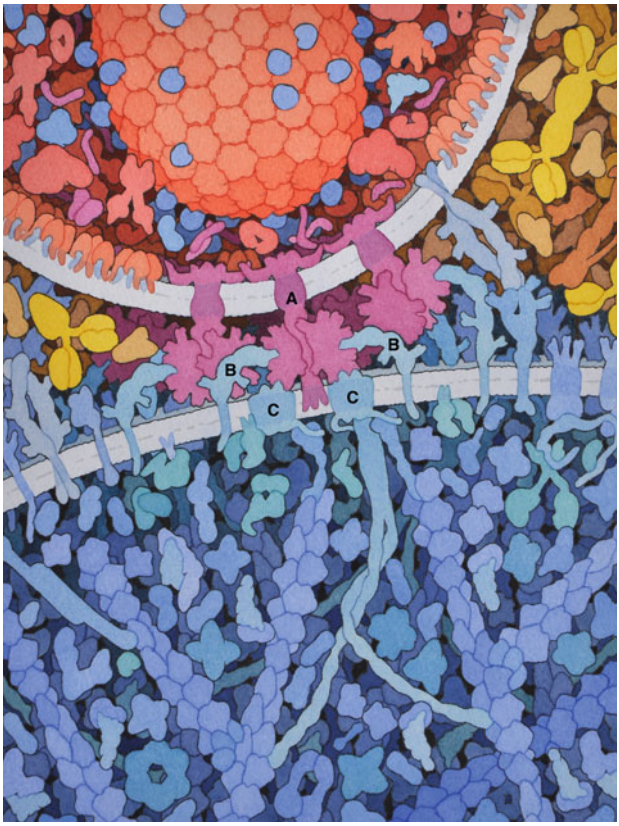
HIV Therapy—The State of ART

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