

# TABLE OF CONTENTS

<b>0. Executive Summary .....</b>	<b>15</b>
<b>1. Introduction to Virology .....</b>	<b>17</b>
<b>Introduction .....</b>	<b>17</b>
<b>Virus databases .....</b>	<b>17</b>
A practical classification of viruses .....	17
<b>Pathomechanism of viral diseases relevant to therapy .....</b>	<b>18</b>
Intrinsic host defense against retroviruses .....	19
Life cycle of virus as basis for antiviral approaches.....	20
Genetic switch in virus infections .....	20
<b>Emerging viruses .....</b>	<b>21</b>
<b>Viral-induced cancer .....</b>	<b>21</b>
<b>Viral encephalitis .....</b>	<b>22</b>
<b>Prophylaxis versus therapy.....</b>	<b>23</b>
<b>Economic impact of viral diseases .....</b>	<b>23</b>
<b>Historical landmarks in the development of antiviral therapies .....</b>	<b>24</b>
<b>2. Antiviral Approaches .....</b>	<b>25</b>
<b>Classification .....</b>	<b>25</b>
<b>Antiviral drug discovery and development.....</b>	<b>25</b>
Viral versus cellular targets for antiviral therapy .....	25
Antivirals based on double-stranded RNA activated caspase oligomerizer.....	27
<b>Antimicrobial peptides .....</b>	<b>27</b>
<b>Immunological approaches.....</b>	<b>28</b>
Basics of immune regulation in relation to viruses.....	28
<i>Effect of viruses on the immune system.....</i>	<i>28</i>
<i>Latent viral infections and the immune system .....</i>	<i>29</i>
Immunomodulating agents .....	29
<i>Amplification of innate immunity.....</i>	<i>29</i>
<i>Blocking the effects of thromboxane A2 on thromboxane receptor .....</i>	<i>29</i>
<i>Enhancers of immune system.....</i>	<i>30</i>
<i>Promoting immune-mediated clearance of a chronic viral infections.....</i>	<i>30</i>
<i>Immunoglobulins .....</i>	<i>30</i>
<i>Bovine lactoferrin.....</i>	<i>31</i>
<i>Quercetin.....</i>	<i>31</i>
Monoclonal antibodies .....	32
<i>Bavituximab .....</i>	<i>32</i>
<i>Treatment of viral infection with radiolabeled MAbs .....</i>	<i>33</i>
<i>Limitations of MAbs and measures to overcome these .....</i>	<i>33</i>
Interferon-based approaches.....	33
<b>Novel antiviral approaches .....</b>	<b>34</b>
Squalamine.....	34
Synthetic modified hypericin compounds.....	34
Targeting Toll-like receptors.....	34
<i>Potential and drawbacks of TLR-ligands in viral diseases .....</i>	<i>35</i>
<b>Inhibition of viral transport from cytoplasm into the cell nucleus.....</b>	<b>36</b>
<b>Nitric Oxide based antiviral therapeutics .....</b>	<b>36</b>
<b>Amino acid cognate anticodon binding specificity.....</b>	<b>36</b>
<b>Antisense approaches to viral infections.....</b>	<b>37</b>
Antisense oligonucleotides .....	37
Limitations of antisense oligonucleotides as antivirals.....	38
NEUGENE antisense .....	38
<b>Gene therapy for viral infections.....</b>	<b>39</b>
<b>RNAi .....</b>	<b>39</b>
RNAi screens of viral genomes.....	39
RNAi for treatment of viral infections.....	40
Promise and pitfalls of RNAi gene therapy .....	41
<b>Management of rapidly evolving pathogens.....</b>	<b>41</b>
<b>Personalized medicine and viral diseases .....</b>	<b>41</b>
<b>An integrated approach to viral diseases .....</b>	<b>41</b>
<b>Current problems and needs in antiviral therapy .....</b>	<b>42</b>
<b>3. Vaccines for Virus Infections .....</b>	<b>45</b>
<b>Introduction .....</b>	<b>45</b>
<b>Types of vaccines.....</b>	<b>46</b>
Live attenuated virus vaccines .....	46
DNA vaccines .....	46

Nanotechnology-based vaccines.....	47
Recombinant viral vaccines .....	48
Synthetic peptides as vaccines .....	48
Virosomes.....	49
Vaccines based on reverse genetics.....	49
Virus-like particles .....	49
<b>Routine vaccination in children against viral infections .....</b>	<b>50</b>
<b>Personalized vaccines.....</b>	<b>50</b>
<b>Limitations of vaccines .....</b>	<b>50</b>
Neurological complications of vaccination.....	51
<b>Expert opinion on antiviral vaccines .....</b>	<b>51</b>
<b>4. Role of Nanotechnology in Developing Antiviral Agents.....</b>	<b>53</b>
<b>Introduction .....</b>	<b>53</b>
Study of interaction of nanoparticles with viruses.....	53
<b>Nanoparticle antiviral agents.....</b>	<b>54</b>
Silver nanoparticles.....	54
Fullerenes.....	54
<b>Nanoviricides.....</b>	<b>55</b>
Role of micelles in nanopharmaceuticals .....	55
Some physicochemical characteristics common to polymeric micelles .....	55
Structure and function of nanoviricides .....	56
<i>Mechanism of action of NanoViricides .....</i>	<i>56</i>
<i>Advantages of NanoViricides.....</i>	<i>57</i>
<b>5. Delivery of Antivirals .....</b>	<b>59</b>
<b>Introduction .....</b>	<b>59</b>
<b>Methods of delivery of antiviral agents.....</b>	<b>59</b>
Local application of antivirals.....	59
Systemic delivery of protein-polymer antiviral drugs.....	60
Controlled delivery of antivirals.....	60
Targeted delivery of antivirals .....	60
Delivery of antivirals to the brain across the blood-brain barrier .....	61
<b>Antiviral vaccine delivery systems.....</b>	<b>61</b>
Minicell vaccine delivery.....	61
Transnasal delivery of vaccines by Newcastle disease virus as vector .....	61
Transdermal delivery of vaccines .....	62
<i>CELLECTRA® electroporation device.....</i>	<i>62</i>
<i>Intramuscular electroporation for delivery of DNA vaccine.....</i>	<i>62</i>
<i>HIV/AIDS vaccination by transdermal application .....</i>	<i>62</i>
<i>Transdermal vaccines for influenza.....</i>	<i>63</i>
<b>Use of nanotechnology for improving delivery of antivirals .....</b>	<b>63</b>
Macrophage-based nanoformulated antiretroviral therapy .....	64
Improvement of antiviral vaccine delivery by nanotechnology.....	65
<i>Bacterial spores for delivery of vaccines.....</i>	<i>65</i>
<i>Chitosan-derived nanoparticles for vaccine delivery .....</i>	<i>65</i>
<i>Gold nanorods for delivery of RNA immune activator molecules .....</i>	<i>65</i>
<i>Lipid nanoparticles for immunostimulatory RNA delivery .....</i>	<i>65</i>
<i>Liposomal antiviral vaccine preparations .....</i>	<i>66</i>
<i>Nanoparticles for DNA vaccines.....</i>	<i>66</i>
<i>Nanospheres for controlled release of viral antigens .....</i>	<i>66</i>
<i>Proteosomes™ as vaccine delivery vehicles .....</i>	<i>67</i>
<i>Polymeric micellae for delivery of DNA vaccine .....</i>	<i>67</i>
<i>"Smart" nanoparticles for delivery of vaccines .....</i>	<i>67</i>
Nanocoating for local viricidal effect .....	68
<b>Delivery of gene-based antiviral drugs .....</b>	<b>68</b>
<b>Limitations of delivery of gene, RNAi and antisense therapies.....</b>	<b>68</b>
<b>Systemic delivery of NanoViricides .....</b>	<b>69</b>
<b>Concluding remarks on delivery of antiviral agents .....</b>	<b>69</b>
<b>6. Competitive Assessment of Antiviral Approaches .....</b>	<b>71</b>
<b>Introduction .....</b>	<b>71</b>
<b>An ideal antiviral agent.....</b>	<b>71</b>
<b>SWOT analysis .....</b>	<b>71</b>
<b>Concluding remarks.....</b>	<b>74</b>
<b>7. Influenza Viruses.....</b>	<b>75</b>
<b>Introduction .....</b>	<b>75</b>
<b>Clinical features of influenza.....</b>	<b>75</b>
Colds due to rhinovirus.....	75

Effects of influenza on the respiratory system.....	76
Effect of avian influenza on the nervous system.....	76
<b>Epidemiology .....</b>	<b>76</b>
Supermap of avian influenza .....	76
Influenza A .....	77
Avian influenza affecting humans.....	77
Human influenza versus avian influenza.....	78
H1N1 influenza .....	79
<b>Immune system and influenza.....</b>	<b>80</b>
Immune Epitope Database and Analysis Resources .....	80
<b>Anti-influenza approaches .....</b>	<b>81</b>
Pharmaceuticals.....	81
Neuraminidase inhibitors .....	81
<i>Mechanism of action.....</i>	<i>81</i>
<i>Tamiflu .....</i>	<i>82</i>
<i>Zanamivir .....</i>	<i>82</i>
<i>CS-8958 .....</i>	<i>82</i>
<i>Peramivir .....</i>	<i>83</i>
<i>Resistance to neuraminidase inhibitors .....</i>	<i>83</i>
<i>Adverse effects of neuraminidase inhibitors.....</i>	<i>84</i>
Other drugs for influenza .....	85
<i>Adamantanes .....</i>	<i>85</i>
<i>Probenecid.....</i>	<i>85</i>
Current recommendations for the use of antiviral agents for influenza .....	85
Vaccines .....	86
<i>Seasonal influenza vaccines .....</i>	<i>86</i>
<i>Live attenuated influenza vaccine vs. inactivated vaccine .....</i>	<i>86</i>
<i>Vaccines for H1N1 influenza .....</i>	<i>87</i>
Current status of influenza vaccines .....	88
<i>Current recommendations for influenza vaccination.....</i>	<i>88</i>
<i>Current status of vaccine preparedness against seasonal influenza.....</i>	<i>88</i>
<i>Current status of vaccine preparedness against H5N1.....</i>	<i>89</i>
Limitations, needs and challenges of influenza vaccines.....	89
<i>Limitations of current influenza vaccines .....</i>	<i>89</i>
<i>Needs of influenza vaccines.....</i>	<i>90</i>
<i>Problems with demand and supply of influenza vaccines .....</i>	<i>91</i>
<i>Problems with access to virus samples.....</i>	<i>91</i>
<i>FluVac project for development of pandemic influenza vaccine.....</i>	<i>91</i>
<i>Influenza vaccines for multiple strains of the disease.....</i>	<i>92</i>
<i>Universal influenza vaccines .....</i>	<i>92</i>
<i>Future prospects of influenza vaccines .....</i>	<i>92</i>
Application of new technologies for influenza vaccines .....	93
Adjuvants .....	93
<i>Cell culture-derived influenza vaccines.....</i>	<i>94</i>
<i>DNA vaccines for avian influenza.....</i>	<i>95</i>
<i>Epitope-based vaccines for influenza .....</i>	<i>95</i>
<i>Gene-based vaccines for influenza .....</i>	<i>96</i>
<i>Live attenuated vaccines.....</i>	<i>96</i>
<i>MABs for passive immunization against avian influenza.....</i>	<i>96</i>
<i>M2e-based human influenza A vaccine.....</i>	<i>97</i>
<i>Pre-pandemic split antigen H5N1 vaccine.....</i>	<i>97</i>
<i>Recombinant-protein based influenza vaccines .....</i>	<i>98</i>
<i>Synthetic avian influenza vaccine.....</i>	<i>99</i>
<i>Viral vectors for influenza vaccination .....</i>	<i>99</i>
<i>Virus-like particles as influenza vaccines .....</i>	<i>99</i>
RNAi-based approaches .....	100
<i>Inhibition of influenza virus by siRNAs .....</i>	<i>100</i>
<i>Limitations of RNAi approach to influenza.....</i>	<i>101</i>
<i>Challenges and future prospects of siRNAs for influenza.....</i>	<i>101</i>
Antisense approaches.....	102
<i>NEUGENE® antisense for inhibition of multiple strains of influenza A.....</i>	<i>102</i>
Nanoviricides against influenza .....	102
Other innovative approaches .....	103
<i>Abatacept .....</i>	<i>103</i>
<i>Polymeric coatings to inactivate influenza virus.....</i>	<i>103</i>
<i>Cytotoxic therapy.....</i>	<i>104</i>
<i>Cyanovirin .....</i>	<i>104</i>
<i>Fludase.....</i>	<i>104</i>
<i>Multiferon®.....</i>	<i>104</i>
<i>Pyrrolidine dithiocarbamate.....</i>	<i>105</i>
<i>T-705.....</i>	<i>105</i>

<i>Value of antivirals in preventing spread of influenza after exposure</i> .....	105
<i>Resistance to influenza therapy and efforts to overcome it</i> .....	106
NIAID Centers of Excellence for research on pandemic influenza viruses .....	106
Research on influenza viruses at Bayer .....	107
Concluding remarks and future prospects.....	107
<b>8. AIDS/HIV .....</b>	<b>109</b>
<b>Introduction .....</b>	<b>109</b>
<b>Epidemiology .....</b>	<b>109</b>
<b>Current concepts of pathomechanisms .....</b>	<b>109</b>
Decoding the structure of an entire HIV genome .....	110
Genetic basis of resistance against HIV .....	110
Host-pathogen interactions that regulate HIV-1 replication.....	110
Pathogenesis of AIDS .....	111
Visualization of the interaction of HIV-1 proteins with target cells .....	112
Viral latency in HIV .....	112
<b>Complications of AIDS .....</b>	<b>113</b>
AIDS and the nervous system .....	113
Opportunistic infections in AIDS.....	113
Coexistent HIV-1 and HSV-2 .....	114
Coexistent hepatitis virus infections with HIV .....	114
<i>HIV and HBV</i> .....	115
<i>HIV and HCV</i> .....	115
AIDS wasting syndrome.....	116
<b>Current therapies.....</b>	<b>116</b>
Aim of anti-HIV drugs.....	117
Efavirenz .....	118
Tipranavir .....	118
Enfuvirtide .....	119
Darunavir .....	119
<b>Impact of antiretroviral treatment on transmission of HIV.....</b>	<b>119</b>
<b>Postexposure prophylaxis against HIV .....</b>	<b>120</b>
<b>Limitations of current therapies.....</b>	<b>121</b>
Adverse effects of antiretroviral therapy .....	121
Drug resistance in AIDS.....	122
Effect of interruption of HIV treatment.....	123
Reservoirs of HIV Infection.....	123
Persistence of low-level viremia in HIV-1 patients on retroviral therapy .....	123
<b>Reconsideration of abandoned therapies for AIDS.....</b>	<b>123</b>
<b>Therapies in development.....</b>	<b>123</b>
Drugs in development for HIV/AIDS .....	124
Nucleoside reverse transcriptase inhibitors .....	125
<i>Apricitabine</i> .....	125
Non-nucleoside reverse transcriptase inhibitors .....	125
<i>Etravirine</i> .....	125
<i>IDX899</i> .....	125
Novel protease inhibitors .....	126
<i>Overcoming HIV-1 resistance to PIs</i> .....	126
<i>PPL-100</i> .....	127
Entry inhibitors targeting CCR5 receptor .....	127
<i>Maraviroc</i> .....	128
<i>SP-01A</i> .....	128
<i>MAbs targeting CCR5 receptor</i> .....	128
<i>PRO 140</i> .....	129
<i>Ibalizumab</i> .....	129
Integrase inhibitors .....	130
<i>Raltegravir (Isentress)</i> .....	130
<i>Elvitegravir</i> .....	131
<i>Dolutegravir</i> .....	131
<i>S/GSK1265744</i> .....	132
<i>LEDGINS</i> .....	132
Design of fusion inhibitor peptides against enfuvirtide-resistant HIV-1 .....	132
Maturation inhibitors .....	132
Blocking of pre-integration complex translocation .....	133
Immune enhancers .....	133
Pyrimidinediones.....	134
Novel combinations of drugs for prevention of AIDS .....	134
<i>Truvada</i> .....	134
<i>Combination of raltegravir, enfuvirtide, and darunavir</i> .....	134
<b>Other innovative antiviral approaches against HIV/AIDS .....</b>	<b>135</b>
Enhancing immune response by blockade of PD-1 receptor .....	135

IL-2 as adjunct to antiretroviral therapy .....	135
A filtration device for HIV-1 as an adjunct to the immune system .....	135
In vitro evaluation of antiviral drug activity .....	135
Methods for sustaining antiviral activity .....	136
Selective targeting of ITK to block multiple steps of HIV replication .....	136
Drugs from natural sources .....	137
Anti-HIV activity of drugs that stimulate cholesterol efflux .....	137
Antiviral hyperactivation-limiting therapeutics .....	137
Blocking of HIV budding by DC-SIGN protein .....	138
ATR kinase as a target for anti-HIV drug discovery .....	138
Nanoviricides for HIV/AIDS .....	138
Prophylactic measures to prevent HIV infection .....	139
Microbicidal agents for local application in HIV/AIDS .....	139
<i>Investigational microbicides against HIV and their limitations</i> .....	140
<i>CCR5 receptor blockers</i> .....	140
<i>PSC-Rantes and recombinant chemokine analogs</i> .....	141
<i>HIV-1 entry inhibitor griffithsin as a topical microbicide</i> .....	141
<i>Nanotechnology-based topical microbicides</i> .....	141
<i>Next generation microbicides for HIV</i> .....	142
<i>Vaginal microbicide containing anti-HIV compound HI-443</i> .....	142
Intracellular immunization in HIV .....	142
<i>Engineered cellular proteins such as soluble CD4s</i> .....	143
<i>Intracellular antibodies</i> .....	143
<i>Selection of T-cell vaccine antigens</i> .....	143
<i>Glycoprotein 120 as target for neutralizing HIV-1 antibodies</i> .....	143
<i>Anti-rev single chain antibody fragment</i> .....	144
Gene therapy strategies in HIV/AIDS .....	144
<i>Inhibition of HIV-1 replication by lentiviral vectors</i> .....	144
<i>VRX496 (Lexgenleucel-T)</i> .....	145
<i>Insertion of protective genes into target cells</i> .....	145
<i>Use of genes to chemosensitize HIV-1 infected cells</i> .....	145
<i>Autocrine interferon-<math>\beta</math> production by somatic cell gene therapy</i> .....	146
HIV/AIDS vaccines .....	146
<i>Cell-based vaccines for HIV</i> .....	146
<i>Delivery of HIV vaccine by an adenoviral vector</i> .....	147
<i>DNA vaccines for HIV/AIDS</i> .....	148
<i>Epitope-based DNA vaccines against HIV</i> .....	149
<i>Gene transfer for HIV vaccination</i> .....	149
<i>Limitations and needs of HIV vaccines</i> .....	149
<i>Recombinant HIV proteins</i> .....	150
<i>Vaccination after discontinuation of antiretroviral treatment</i> .....	150
Innovations in HIV/AIDS vaccine .....	150
<i>Attenuated rabies virus-based vaccine for HIV</i> .....	150
<i>Dendritic cell-based vaccine for HIV</i> .....	151
<i>DermaVir</i> .....	151
<i>Early control of HIV by an effector memory T cell vaccine</i> .....	152
<i>MVA nef vaccine</i> .....	152
<i>Peptide-based vaccine for HIV</i> .....	152
<i>Personalized vaccine for HIV</i> .....	152
<i>RV144 HIV vaccine trial</i> .....	153
<i>Transdermal nanoparticles for immune enhancement in HIV</i> .....	153
<i>Vaccine to prevent HIV entry at the mucosal level</i> .....	153
Cell therapy for HIV/AIDS .....	154
<i>hESCs converted to T-cells for treatment of HIV infection</i> .....	154
<i>Transplantation of genetically modified hematopoietic cells</i> .....	154
<i>Transplantation of genetically modified T cells</i> .....	155
<i>Overlapping Peptide-pulsed Autologous Cells</i> .....	155
Antisense approaches to AIDS .....	156
<i>Antisense oligodeoxynucleotides</i> .....	156
<i>Antisense efforts with PNA constructs</i> .....	156
<i>RNA decoys</i> .....	157
<i>Ribozymes</i> .....	157
RNAi applications in HIV/AIDS .....	158
<i>A multiple shRNA approach for silencing of HIV-1</i> .....	158
<i>Aptamer-mediated delivery of anti-HIV siRNAs</i> .....	158
<i>Bispesific siRNA constructs</i> .....	159
<i>Role of the nef gene during HIV-1 infection and RNAi</i> .....	159
<i>siRNA-directed inhibition of HIV-1 infection</i> .....	159
<i>Synergistic effect of snRNA and siRNA</i> .....	160
<i>Targeting CXCR4 with siRNAs</i> .....	161
<i>Targeting CCR5 with siRNAs</i> .....	161

<i>Concluding remarks on RNAi approach to HIV/AIDS</i> .....	161
Companies involved in developing gene therapy for HIV/AIDS .....	162
Conclusions regarding gene therapy of HIV/AIDS .....	162
<b>Testing for new anti-HIV therapies</b> .....	<b>163</b>
<b>Personalized approach to management of HIV</b> .....	<b>163</b>
Differences in response of the body to HIV .....	163
Variations in action of drugs on HIV .....	164
<i>Drug-resistance in HIV</i> .....	164
<i>Replication Capacity measurement</i> .....	164
<i>Role of biomarkers in management of HIV/AIDS</i> .....	165
<i>Role of diagnostic testing in management of HIV</i> .....	165
<i>Prevention of adverse reactions to antiviral drugs</i> .....	166
<i>Nanoviricides as a personalized approach to HIV</i> .....	166
<b>Concluding remarks and future prospects</b> .....	<b>166</b>

<b>9. Hepatitis Viruses</b> .....	<b>169</b>
<b>Introduction</b> .....	<b>169</b>
<b>Hepatitis delta virus infection</b> .....	<b>169</b>
<b>Hepatitis A virus infection</b> .....	<b>169</b>
<b>Hepatitis E virus infection</b> .....	<b>170</b>
Epidemiology.....	170
Structure of the HEV .....	170
HEV vaccines.....	170
<b>Epidemiology of HBV</b> .....	<b>171</b>
<b>Pathogenesis of HBV-induced liver disease</b> .....	<b>171</b>
<b>Current approaches to management of HBV</b> .....	<b>172</b>
Entecavir .....	172
Adefovir dipivoxil .....	173
Telbivudine .....	173
Pegylated interferon-alpha .....	173
<b>Limitations of current therapies and needs of HBV</b> .....	<b>173</b>
<b>Personalized management of HBV</b> .....	<b>174</b>
<b>Innovations in the management of HBV</b> .....	<b>174</b>
Tenofovir disoproxil fumarate .....	174
Hepatitis B immune globulins .....	175
<i>Nabi-HB</i> .....	175
<i>HepaGam B</i> .....	175
Hepatitis B vaccine composed in a novel nanoemulsion adjuvant .....	175
Innovative pharmaceuticals for HBV .....	176
<i>Clevudine</i> .....	176
<i>HepDirect prodrugs</i> .....	176
Monoclonal antibodies for HBV.....	177
RNAi-based therapy of HBV.....	177
Personalized treatment of hepatitis B .....	178
Concluding remarks and future prospects of management of hepatitis B .....	178
<b>Epidemiology of HCV</b> .....	<b>178</b>
<b>HCV characteristics</b> .....	<b>179</b>
<b>Pathomechanism of HCV infection</b> .....	<b>179</b>
Mechanism of HCV entry .....	179
HCV and the immune system .....	179
Mechanism of HCV replication and response to interferon.....	180
<b>Current approaches to management of HCV</b> .....	<b>180</b>
Interferon therapy for HCV.....	180
Limitations of current HCV therapies .....	181
<b>Novel approaches to HCV</b> .....	<b>181</b>
HCV protease inhibitors .....	182
<i>Boceprevir</i> .....	182
<i>Narlaprevir (SCH 900518)</i> .....	182
<i>Telaprevir (Incivek)</i> .....	183
<i>Small molecule HCV protease inhibitors</i> .....	183
Innovations in interferon therapy for HCV .....	183
<i>AlbIFN-<math>\alpha</math>2b</i> .....	184
<i>Directed evolution of gene-shuffled IFN-<math>\alpha</math> for treatment of HCV</i> .....	184
<i>GEA007.1</i> .....	184
<i>Omega DUROS</i> .....	184
<i>PEG-IFN-<math>\lambda</math></i> .....	185
<i>Personalizing interferon therapy of HCV</i> .....	185
Innovative ribavirin-based treatments .....	186
<i>Targeted delivery of hemoglobin-ribavirin conjugate for HCV</i> .....	186
<i>Taribavirin</i> .....	186
Nucleoside polymerase inhibitor.....	186

<i>Valopicitabine</i> .....	186
Host cell targets for hepatitis C therapy .....	187
<i>SP-10</i> .....	187
NS5a inhibitors.....	188
NS5b inhibitors.....	188
Compounds targeting HCV receptor E2 .....	188
Cyclophilin inhibitors .....	189
<i>Alisporivir</i> .....	189
Methylene blue.....	190
Naringenin .....	190
Nitazoxanide .....	190
Cyclosporine and analogues as anti-HCV agents .....	191
Clemizole and HCV.....	191
RNAi-based approaches to HCV .....	192
<i>Use of adenoviral vectors for RNAi</i> .....	192
<i>siRNAs for HCV</i> .....	192
<i>Limitations and drawbacks of siRNA therapy for HCV</i> .....	193
<i>Role of miRNA in viral infections</i> .....	193
<i>miR-122 antagonists</i> .....	194
Vaccines for HCV .....	194
<i>Therapeutic vaccine for HCV</i> .....	194
<i>Vaccine based on neutralizing antibodies to HCV</i> .....	194
Clinical trials of HCV therapeutics.....	195
Limitations to the development of effective anti-HCV therapeutics .....	195
<i>Causes of treatment failure in chronic hepatitis C</i> .....	195
<i>HCV drug resistance</i> .....	196
<b>Personalized management of HCV infection.....</b>	<b>196</b>
Role of sequencing in personalized management of HCV .....	197
<b>Concluding remarks about HCV therapy.....</b>	<b>198</b>
<b>Future needs in HCV therapy .....</b>	<b>198</b>

## **10. Miscellaneous Commercially Important Virus Infections ..... 201**

<b>Introduction .....</b>	<b>201</b>
<b>Herpes viruses.....</b>	<b>201</b>
Herpes simplex virus .....	201
Treatment of HSV-1 .....	201
<i>Acyclovir</i> .....	201
<i>Vaccines for HSV</i> .....	202
<i>Antisense therapy for HSV-1</i> .....	202
Herpes simplex virus 2 and genital herpes .....	202
<i>Famciclovir</i> .....	203
<i>Intravaginal microbicial agents for HSV-2</i> .....	203
<i>Vaccines for HSV-2</i> .....	203
Herpes simplex keratitis .....	204
Herpes simplex encephalitis .....	204
Limitations of current HSV therapies .....	205
<b>Herpes zoster virus.....</b>	<b>205</b>
Herpes zoster and chicken pox .....	205
Epidemiology of herpes zoster .....	205
Treatment of herpes zoster .....	206
Herpes zoster vaccine.....	206
<b>Cytomegalovirus.....</b>	<b>206</b>
Current treatment of CMV .....	206
<i>Valganciclovir hydrochloride</i> .....	207
<i>Limitations of current treatment and future prospects</i> .....	207
T-cell therapy for CMV .....	207
Vaccine for CMV.....	207
Gene therapy of CMV .....	208
Antisense approach to CMV .....	208
siRNA treatment of CMV .....	209
<b>Epstein-Barr virus.....</b>	<b>209</b>
<b>Human papilloma virus .....</b>	<b>209</b>
Epidemiology.....	209
Vaccines for HPV.....	210
<i>Gardasil</i> .....	210
<i>Cervarix</i> .....	210
<i>Vaccine based on fusion proteins of HPV envelope</i> .....	211
<i>DNA vaccine VGX-3100</i> .....	211
<i>Limitations of HPV vaccines</i> .....	211
Antivirals for HPV.....	212
<i>Imiquimod</i> .....	212

Novel approaches against HPV.....	212
<i>Intrabody strategies for the treatment of HPV</i> .....	212
<i>A novel peptide to inhibit HPV</i> .....	213
<i>Heat shock protein-based antivirals</i> .....	213
<b>Respiratory syncytial virus .....</b>	<b>214</b>
Epidemiology.....	214
Current management of RSV .....	214
<i>Palivizumab</i> .....	214
Innovative anti-RSV products in development.....	214
<i>RSV604</i> .....	214
<i>MDT-637</i> .....	215
<i>RNAi approach to RSV</i> .....	215
Vaccines for RSV.....	215
<i>BCG as a vaccine against RSV</i> .....	215
<i>Oral DNA vaccine for RSV</i> .....	216
<i>Neutralizing antibodies against preactive form of hRSV_F protein</i> .....	216
<b>Other respiratory viruses.....</b>	<b>216</b>
Parainfluenzavirus type 3.....	216
Human metapneumovirus .....	217
<b>Gastrointestinal viruses .....</b>	<b>217</b>
Noroviruses.....	217
<b>Concluding remarks .....</b>	<b>218</b>
<b>11. Viruses with High Impact but Low Commercial Significance .....</b>	<b>219</b>
<b>Introduction .....</b>	<b>219</b>
<b>Chikungunya fever.....</b>	<b>219</b>
<b>Coxsackie virus.....</b>	<b>219</b>
<b>Japanese encephalitis.....</b>	<b>220</b>
Vaccines for JE .....	220
<b>Parvovirus .....</b>	<b>221</b>
<b>Polyomavirus JC .....</b>	<b>221</b>
<b>Rabies.....</b>	<b>221</b>
Rabies vaccines .....	222
<i>Recombinant viral vaccines for rabies</i> .....	222
DNA vaccine against rabies .....	223
Rabies immune globulin.....	223
Monoclonal antibodies for rabies .....	223
NanoViricides approach for rabies .....	223
The Milwaukee protocol for rabies .....	224
<b>Rotavirus .....</b>	<b>224</b>
Epidemiology.....	224
Vaccines against rotavirus.....	225
<b>Viral hemorrhagic fevers .....</b>	<b>225</b>
Dengue.....	226
<i>Antivirals in development</i> .....	226
<i>Dengue vaccines</i> .....	227
<i>Elimination of dengue vector mosquitoes by fungus</i> .....	228
<i>Genetic elimination of dengue vector mosquitoes</i> .....	228
Ebola virus.....	229
<i>Development of antiviral drugs for Ebola</i> .....	229
<i>DNA vaccine for Ebola</i> .....	229
Lassa fever .....	230
Marburg hemorrhagic fever .....	230
Yellow fever .....	231
<i>Vaccines for yellow fever</i> .....	231
<i>Sequencing of Aedes aegypti genome and control of yellow fever</i> .....	231
Crimean-Congo hemorrhagic fever .....	232
<b>West Nile virus .....</b>	<b>232</b>
Epidemiology.....	232
Pathogenesis.....	233
Treatment of West Nile neuroinvasive disease .....	233
Vaccines against WNV .....	233
Innovative treatments for WNV.....	234
<b>Western equine encephalitis.....</b>	<b>234</b>
<b>Sporadic virus epidemics .....</b>	<b>234</b>
Coronavirus/severe acute respiratory syndrome .....	234
<i>Therapeutic approaches to SARS</i> .....	235
<i>MABs for SARS</i> .....	235
<i>siRNA treatment of SARS</i> .....	236
<b>Zoonotic viral infections .....</b>	<b>236</b>
Vaccines for zoonotic viral diseases .....	236

<b>Virus bioterrorism and biowarfare</b> .....	<b>237</b>
Small pox as a biological weapon .....	237
<i>Status of small pox vaccination</i> .....	237
Strategies against virus bioterrorism and biowarfare .....	238
<i>Increasing resistance by stimulating innate immune mechanisms</i> .....	238
<i>Nanoviricides for combating viral bioterrorism</i> .....	239
<b>Concluding remarks</b> .....	<b>239</b>
<b>12. Markets for Antivirals</b> .....	<b>241</b>
<b>Introduction</b> .....	<b>241</b>
<b>Markets according to disease</b> .....	<b>241</b>
Influenza market .....	241
HIV/AIDS market.....	242
Hepatitis B and C markets.....	243
<b>Markets according to products and approaches</b> .....	<b>243</b>
<b>Market values of monoclonal antibodies for viral diseases</b> .....	<b>243</b>
<b>Market values of vaccines for viral diseases</b> .....	<b>243</b>
Markets for vaccines against HPV.....	244
Markets for other antiviral vaccines.....	244
<b>Markets according to geographical areas</b> .....	<b>245</b>
Emerging markets for antiviral therapeutics .....	245
Geographical distribution of HIV/AIDS market .....	246
<b>Unmet needs in antivirals</b> .....	<b>246</b>
<b>Policies regarding conquered viral diseases</b> .....	<b>247</b>
Future of polio vaccine.....	247
<b>Policies concerning HPV vaccine for prevention of cervical cancer</b> .....	<b>248</b>
<i>HPV vaccine in developing countries</i> .....	248
<b>Future prospects of innovative approaches</b> .....	<b>249</b>
US Government support of antiviral efforts.....	250
<i>US Government support for R &amp; D in avian influenza vaccines</i> .....	250
<i>US Government support for developing anti-bioterrorism agents</i> .....	250
The European Union support of antiviral research .....	251
<i>European Commission's research support for anti-HIV/AIDS programs</i> .....	251
<i>European Commission's support anti-influenza programs</i> .....	252
Collaboration of biotechnology companies with big pharma .....	253
<b>Strategies for marketing</b> .....	<b>253</b>
<b>13. Companies</b> .....	<b>255</b>
<b>Introduction</b> .....	<b>255</b>
<b>Top companies</b> .....	<b>255</b>
<b>Profiles of pharmaceutical companies</b> .....	<b>256</b>
<b>Profiles of antiviral companies</b> .....	<b>272</b>
<b>Profiles of viral vaccine companies</b> .....	<b>386</b>
<b>Collaborations</b> .....	<b>455</b>
<b>14. References</b> .....	<b>461</b>

## Tables

Table 1-1: A practical classification of viruses.....	17
Table 1-2: Viruses causing encephalitis .....	23
Table 1-3: Vaccines vs therapeutics for viral diseases.....	23
Table 1-4: Historical landmarks in the development of antiviral therapies .....	24
Table 2-1: Classification of antiviral strategies.....	25
Table 2-2: Viral vs cellular targets for discovery of antivirals .....	26
Table 2-3: Viruses amenable to antisense oligonucleotides .....	38
Table 2-4: Inhibition of viral replication by RNAi .....	40
Table 3-1: Types of vaccines for viral diseases .....	46
Table 4-1: Role of nanobiotechnology in virology .....	53
Table 5-1: Methods of delivery of antiviral agents .....	59
Table 5-2: Role of nanotechnology for improving delivery of antivirals.....	64
Table 5-3: Commercially available liposomal antiviral vaccines .....	66
Table 6-1: SWOT of monoclonal antibodies .....	71
Table 6-2: SWOT of agents that prevention viral entry into cells .....	72
Table 6-3: SWOT of drugs interfering with intracellular replication .....	72
Table 6-4: SWOT of protease inhibitors .....	72
Table 6-5: SWOT of integrase inhibitors .....	72
Table 6-6: SWOT of maturation inhibitors .....	72
Table 6-7: SWOT of neuraminidase inhibitors .....	73

Table 6-8: SWOT of targeting Toll-like receptors (TLRs).....	73
Table 6-9: SWOT of topical antiviral agents against viral infections.....	73
Table 6-10: SWOT of gene therapy, antisense oligonucleotides, RNAi.....	73
Table 6-11: SWOT of vaccines.....	73
Table 6-12: SWOT of NanoViricides.....	74
Table 7-1: Anti-influenza approaches.....	81
Table 7-2: Antiviral drugs used for influenza.....	81
Table 7-3: Various approaches to production of influenza vaccines.....	93
Table 8-1: Drugs in clinical development for HIV/AIDS.....	124
Table 8-2: Strategies for gene therapy of AIDS.....	144
Table 8-3: Classification of HIV/AIDS vaccines in clinical trials.....	146
Table 8-4: Companies involved in developing gene therapy for HIV/AIDS.....	162
Table 9-1: Innovations in the treatment of HBV.....	174
Table 9-2: Innovations for management of HCV.....	182
Table 9-3: Antiviral agents for HCV targeting host cells.....	187
Table 9-4: HCV drugs in clinical trials.....	195
Table 10-1: Methods of delivery of acyclovir.....	201
Table 11-1: Strategies against virus bioterrorism and biowarfare.....	238
Table 12-1: Worldwide market for all antiviral approaches 2011-2021.....	241
Table 12-2: Markets for antivirals according to virus infections 2011-2021.....	241
Table 12-3: Markets values of all drugs for HIV/AIDS 2011-2021.....	242
Table 12-4: Market values of monoclonal antibodies for viral diseases 2011-2021.....	243
Table 12-5: Market values of vaccines for viral diseases 2011-2021.....	244
Table 12-6: Markets for antiviral drugs according to geographical areas 2011-2021.....	245
Table 12-7: Markets for antiviral vaccines according to geographical areas 2011-2021.....	245
Table 12-8: Emerging markets for antiviral drugs according to countries 2011-2021.....	245
Table 12-9: Emerging markets for antiviral vaccines according to countries 2011-2021.....	246
Table 13-1: Top five antiviral companies.....	255
Table 13-2: Roche antiviral products in development.....	262
Table 13-3: Collaborations of antiviral companies.....	455

## Figures

Figure 1-1: Varieties of host and cell responses to viral infections.....	19
Figure 1-2: Cycle of infection and replication of a retrovirus.....	20
Figure 1-3: Viral-induced cancer.....	22
Figure 2-1: An integrated approach to viral diseases.....	42
Figure 4-1: Schematic representation of NanoViricide attacking a virus particle.....	57
Figure 7-1: Evolution of mutations associated with virulence/drug resistance in H5N1.....	78
Figure 7-2: Mechanism of development of resistance to oseltamivir.....	84
Figure 8-1: Mode of action of some current anti-HIV drugs.....	117
Figure 9-1: Steps of HBV replication and site of action of various drugs.....	171
Figure 9-2: Omega DUROS device for interferon delivery in chronic hepatitis C.....	185
Figure 12-1: Unmet needs in antivirals.....	247