

Index

- A**
- Adaptive immune responses
 - cellular, 486
 - in nonhuman primates, 471
 - simian immunodeficiency viruses (SIVs), 312
 - Adenovirus vectors, 435, 436, 488–490
 - Adjuvants, vaccine, 458
 - Africa
 - epidemic spread of HIV in, 374
 - epidemic trends in, 368–370
 - HIV/AIDS statistics, 370
 - HIV prevalence, 369
 - African green monkeys, 305–315
 - AIDS (acquired immunodeficiency syndrome)
 - epidemic
 - in high-income countries, 385–399
 - in low- to middle-income countries, 367–379
 - first recognition of, 1
 - pandemic, 1–2, 14–15
 - pathogenesis, 188–189
 - Allogeneic transplantation, 346–347
 - Alternative splicing of HIV-1 mRNA, 82–84
 - ALVAC, 492–494
 - Antibody
 - monoclonal, 225
 - neutralizing
 - development of broadly cross-neutralizing antibodies, 219–222
 - response against HIV-1, 217–227
 - role in protection, 448–449
 - vaccine design to elicit, 447–458
 - nonneutralizing, 225–226
 - role in protection, 448–449
 - Antibody response against HIV-1, 217–227
 - development of broadly cross-neutralizing antibodies, 219–222
 - disease progression and, 222–223
 - early antibodies and viral escape, 218–219
 - monoclonal antibodies, 225
 - nonneutralizing antibodies, 225–226
 - overview, 217–218
 - transmission and, 223–225
 - Antiretroviral therapy (ART), 321–337. *See also specific drugs; specific therapies*
 - basic principles, 321–324
 - central nervous system (CNS) disease, 294–297
 - beneficial effects, 294–295
 - penetration of cART, 296–297
 - persistent evidence of HAND despite therapy, 295–296
 - entry inhibitors, 332, 335–336
 - fusion inhibitors, 332, 335
 - small-molecule CCR5 antagonists, 335–336
 - FDA approval, timeline for, 322
 - integrase inhibitors, 330–332
 - microbicides, 505–519
 - mucosal immune system and, 201–202
 - nonnucleoside reverse transcriptase inhibitors (NNRTIs)
 - mode of action, 514
 - overview, 329–330, 513–514
 - resistance, 51, 329–330
 - structure, 329
 - nucleoside reverse transcriptase inhibitors (NRTIs)
 - mode of action, 327, 513
 - overview, 327–328, 512–513
 - resistance mechanisms, 327, 328
 - resistance mutations, 51, 327–328
 - structure, 51, 328
 - oral preexposure prophylaxis (PrEP), 524–528
 - to prevent initial events in mucosal transmission, 507–511
 - prevention in discordant couples, 545
 - protease inhibitors, 332, 333
 - resistance to ARV-based microbicides, 517–518
 - targets in viral life cycle, 324–327, 508–509
- Antisense RNA, 348–349
- APOBEC proteins, 48, 121–125
 - APOBEC3F (A3F), 124
 - APOBEC3G (A3G), 121–124, 125
 - described, 121–122
 - domain organization, 122
 - regulation of, 125
 - Vif inhibition of function, 123–124
 - viral hypermutation and, 122–123
 - APOBEC3H (A3H), 124
- identification, 121
- natural HIV-1 infections and, 125
- overview, 121–122
- Aptamers, 349
- ARV (antiretroviral) drugs. *See* Antiretroviral therapy (ART)

Index

Asia

- epidemic spread of HIV to, 374–376
- epidemic trends in, 371
- HIV/AIDS statistics, 370
- HIV prevalence, 369

Assembly, 95–103

- immature particles, 101–103
- location of, 109
- overview, 95–96, 97
- peptide assembly inhibitor (CAI), 102
- protein trafficking and virion incorporation, 98–99
- RNA packaging, 96–98
- RNA trafficking and incorporation, 99–101
- viral lipid composition, 99
- virion composition, 96–98

Avian sarcoma-leukosis virus (ASLV), 40

B

Baltimore, David, 37

BAT-24 dosing, 515, 516

B-cell responses, in nonhuman primates, 471–472

- behavioral strategies for prevention, 539–542
- behavioral intervention programming, 540
- behavioral intervention research, 539, 540
- condoms, 542–544
- list of, 540
- need for combination prevention, 540, 542

“Berlin Patient,” 350–351

Biomarkers of central nervous system (CNS) disease, 293–294

Blood

- dissemination and persistence in, 166–167
- risk exposure from administration of, 396–397

Breast, pathogenesis in, 170

Budding

- assembly of core ESCRT machinery, 104–105
- blocks to release, 106
- late domains and ESCRT pathway recruitment, 103–104
- membrane bridges, 111
- models of membrane fission, 105–106
- sites of release, 109–111
- viral lipid composition, 99
- virological synapse, 109–111

C

CA (Gag domain), HIV-1 assembly and, 101–103

Canarypox vectors, 492–494

Cancer and insertional activation of proto-oncogenes, 70

Capsid

- fullerene cone model, 106–108
- structure, 106–108

Caribbean

- epidemic trends in, 371–372
- HIV/AIDS statistics, 370

Caspase 8, 170

Caspase 9, 170

CCR5

- antagonists, 511–512
- CCR5 Δ 32 mutation, 350–351
- expression in CD4⁺ T cells, 162
- microbicide targeting of, 511–512
- signal transduction through, 31
- as treatment target, 350–355
 - “Berlin Patient,” 350–351
 - gene-editing strategies, 352–355
 - gene therapy to reduce expression, 352
 - HIV latency and, 351–352
 - small-molecule CCR5 antagonists, 335–336
- viral entry and, 24–31

CD4

- discovery of, 25
- signal transduction through, 30–31
- viral entry and, 23–32

CD4bs immunogens, 455, 456

CD4⁺ T cells

- CCR5 expression, 162
- cell-to-cell transmission of HIV-1, 110, 111
- CXCR4 expression, 162–163
- dendritic cell–mediated transfection of, 28–29
- early events in replication, 161–162
- HIV-1 latency in, 267–280
- mechanism of cell killing, 170
- responses in acute and chronic infection, 239–240
- in target tissues, 164, 166–167

CD8⁺ T cells

- evolution following acute infection, 238–239
- functions in HIV infection, 245–246
- immune pressure and viral escape, 240–242
- immunogenetics of HIV-specific responses, 242–245
- responses in acute infection, 236–238
- vaccine design for response of, 431–440

CD26, 25

Cell-to-cell transmission, 110, 111

Central nervous system (CNS), 287–299

- antiretroviral therapy (ART), 294–297
 - beneficial effects, 294–295
 - penetration of cART, 296–297
 - persistent evidence of HAND despite therapy, 295–296
- antiretroviral therapy for disease, 294–297
- biomarkers of disease, 293–294
- compartmentalization, 291–292
- mechanism of injury, 292
- strain-specific neuropathogenesis, 292–293
- viral entry and maintenance of infection in, 288–291
- virus in, 167–168

- Chemokine receptors, 420
- Chemokines, 420
- Chimpanzees
 - chimpanzee endogenous retrovirus-1 and -2 (CERV1 and CERV2), 422
 - SIVcpz
 - acquisition by predation, 7
 - HIV-1 origins and, 8–11
 - natural history of infection, 7–8
 - origin and distribution, 5–7
 - species and subspecies, 5
- Chromatin
 - compaction around integrated HIV-1 provirus, 271
 - HIV-1 latency and, 270–272
- Circulating recombinant forms (CRFs)
 - in high-income countries, 387–388
 - in low- and middle-income countries, 377–378
- Circumcision, male, 547–549
- Clades, of HIV, 387–388
- Clinical manifestations of infection, 194–195
- Clinical trials. *See* Trials
- Combination antiretroviral therapy (cART)
 - for central nervous system (CNS) disease, 294–297
 - CNS penetration of, 296–297
- Condoms, 542–544
- Coreceptor. *See also* CCR5; CXCR4
 - microbicides inhibition of coreceptor interaction, 511–512
- Counseling, 544
- CXCR4
 - discovery of, 26
 - expression in CD4⁺ T cells, 162–163
 - signal transduction through, 31
 - viral entry and, 24–29, 31
- Cytokine storm, 256
- Cytomegalovirus (CMV), MHC class I homologs and, 258
- Cytotoxic T lymphocytes (CTLs)
 - evolution following acute infection, 238–239
 - immune pressure and viral escape, 240–242
 - immunogenetics of HIV-specific responses, 242–245
 - responses in acute infection, 236–238
 - response to HIV, 235–247
- D**
- Dapivirine
 - mode of action, 514
 - sustained drug delivery, 515
- Data integration, 423
- Dementia, HIV-1-associated, 287, 290, 293–295, 298
- Dendritic cells
 - hormonal sensitization of, 256
 - interferon production by, 256
 - transfection of CD4⁺ T cells, 28–29
 - vaccine targeting and, 436–437
- Disease progression, antibodies and, 222–223
- DNA
 - breaking and joining reactions in integration, 61
 - integration, 59–71
 - transposition, integration similarity to, 62–63
 - vaccine, 433–434, 487–488
 - vaccines, 433–434
- DNA methylation, HIV-1 latency and, 272
- Drift, 185–186
- Drug-resistant HIV
 - in high-income countries, 390–392
 - in low- and middle-income countries, 377–378
- E**
- Eclipse phase, 177, 486
- Entry, 23–32
 - fundamentals of, 23–25
 - key recent advances, 26–30
 - cell–cell transfer, 28–29
 - location of entry, 27–28
 - structural information, 26–27
 - virological synapse, 28–29
 - microbicides targeting of viral entry, 511
 - nervous system, 288–291
 - receptors, discovery of, 25–26
 - signal transduction, 30–32
 - CCR5 and CXCR4, 31–32
 - CD4, 30–31
 - HIV Env, 30
- Entry inhibitors, 332, 335–336
 - fusion inhibitors, 332, 335
 - small-molecule CCR5 antagonists, 335–336
- Env
 - CXCR4 and, 162–163
 - signal transduction mediated by, 30
 - tetherin antagonism by, 129
 - as vaccine target, 437–438, 447–458
 - viral entry and, 23–32
- Epidemic, HIV-1
 - in high-income countries, 385–399
 - drug-resistant HIV and transmission, 390–392
 - prevention of HIV, 399
 - risk exposures, 392–398
 - transmission networks and dynamics, 391–392
 - virus diversity in Northern Hemisphere, 388–390
 - virus evolution and rates if change, 386–390
 - in low- to middle-income countries, 367–379
 - consequences of HIV genetic diversity on vaccine development, 378–379
 - current status, 368–372
 - epidemiological history, 368
 - genetic diversity and drug resistance, 377–378
 - HIV pathogenesis, 376–377
 - molecular epidemiology, 372–376

Index

- Epidemic, HIV-1 (*Continued*)
 spread of HIV in Africa, 374
 spread of HIV to Asia and the Pacific Rim, 374–376
 spread of HIV to South America, 374
 trends in Africa, 368–370
 trends in Asia, 371
 trends in Latin America and the Caribbean, 371–372
- Epidemiology
 epidemic
 in high-income countries, 385–399
 in low- to middle-income countries, 367–379
 molecular, 372–376, 391–392
- Epigenetic regulation of HIV-1 transcription, 82
- Epitope escape, 439
- Eradication, latency and, 279–280
- ESCRT (endosomal sorting complexes required for transport)
 assembly of core machinery, 104–105
 blocks to HIV-1 release, 106
 membrane fission models and, 105–106
 recruitment, 103–104
- Europe, viral diversity in, 388–390
- Evasion, mechanisms of, 123
- Evolution
 course following infection, 186–188
 of cytotoxic T lymphocytes (CTLs) following acute infection, 238–239
 factors in HIV-1 evolution, 184–186
 drift, 185–186
 linkage, 186
 mutation, 184–185
 of host range variants, 165
 of host restriction factors, 13
 killer immunoglobulin-like receptors (KIRs) as driver of, 262–263
 lentiviruses, 4–5
 overview of viral, 386–390
 major clades, 387–388
 viral diversity in Northern Hemisphere, 388–390
 rate of HIV-1, 14–15
 of tetherin and viral antagonists, 13, 130
 viral diversity in Northern Hemisphere, 388–390
 Europe 1980-1990, 388–390
 Europe 1990-2005, 390
 North America, 388
 “viral fossils,” 4
- Evolutionary genomics, 422
- F**
- FDA drug approval, timeline for, 322
- Female condom, 543
- Founder virus, 161
- Frameshifting, 88
- Fullerene cone model for HIV-1 capsid, 106–108
- Fusion inhibitors, 332, 335, 348
- G**
- Gag polypeptide
 protein trafficking and virion incorporation, 98–99
 structure, 95–96
 as vaccine target, 437
 virion assembly, budding, and maturation, 95–111
- Gag-Pro-Pol polyprotein, protein trafficking and virion incorporation of, 98–99
- GALT (gut-associated lymphoid tissue), dissemination and persistence in, 167
- Gene-editing strategies, 352–355
- Gene expression, 77–89
 alternative splicing of HIV-1 mRNA, 82–84
 early and late phases of mRNA expression, 85
 frameshifting, 88
 guiding of transcripts through the cytoplasm, 87
 nuclear retention of mRNAs, 87
 processing and polyadenylation of RNA, 87–88
 transcription control by Tat, 77–82
 discovery of transactivation by Tat, 77–79
 epigenetic regulation, 82
 LTR as a promoter, 81–82
 P-TEFb, regulation of, 81
 P-TEFb as cofactor for Tat, 79–80
 Tat/TAR RNA interaction, 79
 transactivation mechanism, 80–81
 transcriptional feedback, 82
 translation initiation, 88
- Gene therapy to reduce CCR5 expression, 352
- Genetic diversity
 consequences on vaccine development, 378–379
 drug resistance and, 377–378
- Genetic variation, 184–188
- Genital tract, virus in, 168
- Genome-wide association studies (GWASs), 410–413
- Genomics, 410–416
 advanced genome analyses, 414–416
 data integration, network, and systems biology, 423
 evolutionary, 422
 genome-wide association studies (GWASs), 410–413
 joint viral-host analysis, 420–421
 next-generation sequencing, 421–422
 primate genetics, 416–420
 vaccine genomics, 413–414
- Glycan immunogens, 455–457
- Gorilla (SIVgor)
 distribution, 6, 8
 HIV-1 origins and, 9–10
 origin, 8
- Gp120 vaccines, 449

Gut-associated lymphoid tissue (GALT), dissemination and persistence in, 167
GWASs (genome-wide association studies), 410–413

H

HAART. *See also* Antiretroviral therapy (ART)
latency and, 276–280
role of inflammation/activation in complications of treated infection, 205–207
HAD (HIV-1-associated dementia), 287, 290, 293–295, 298
HAND (HIV-associated neurocognitive disorders), 288, 292–295, 297, 298
HCT (HIV counseling and testing) services, 544
Hematopoietic stem cells, pathogenesis in, 169–170
Herpes simplex 2, 550
HERV (human endogenous retroviruses), 438
Heterochromatin, HIV-1 latency and, 271–272
Heterosexual spread, 397–398
HIV-1
acute infection, 138–140
antibody response against, 217–227
assembly, budding, and maturation, 95–111
DNA integration, 59–71
epidemic
in high-income countries, 385–399
in low- to middle-income countries, 367–379
evolution rate, 14–15
gene expression, regulation of, 77–89
latency in CD4⁺ T cells, 267–280
lineages (groups M, N, O, and P), 9–10
origins, 8–11
reverse transcription, 37–51
transmission
clinical event, 138–140
population bottleneck to, 140–144
routes and risks for, 136–138
HIV-1-associated dementia (HAD), 287, 290, 293–295, 298
HIV-2
lineages of, 11
natural history of infection, 11
origins, 11, 12
HIV-associated neurocognitive disorders (HAND), 288, 292–295, 297, 298
HIV counseling and testing (HCT) services, 544
HIV drug resistance (HIVDR)
in different subtypes, 377–378
surveillance in antiretroviral treatment-naive infected individuals, 377
transmitted HIV drug resistance (TDR), 377
HLA-A, down-regulation of, 257
HLA-B, down-regulation of, 257
Human endogenous retroviruses (HERV), 438

Human tissue explant model of HIV transmission, 150–151
Humoral immune response during HIV-1 infection, 450

I

Iatrogenic exposure, as risk exposure, 396–397
Immune activation, role in disease pathogenesis, 202–203
Immunogen design, 455–458
B-cell biology and, 457–458
CD4bs immunogens, 455, 456
CD4i region, 457
glycan and quaternary immunogens, 455–457
MPER region, 457
V3 region, 457
Infection. *See also* Pathogenesis
clinical manifestations of, 194–195
early targets of, 198–199
evolution of HIV after, 186–188
role of inflammation/activation in complications of treated infection, 205–207
time course of HIV-1, 164, 177–179
Injection drug use
prevention among users, 550–553
as risk exposure, 395–396
Innate immunity
cells involved, 256–257
cytokine storm, 256
NK cells, 257–263
HIV evasion through Nef, 257–258
in nonhuman primates, 470–471
overview of system, 255–256
pattern recognition receptors, 255
simian immunodeficiency viruses (SIVs), 312–313
Insertional activation of proto-oncogenes, 70
Integrase inhibitors, 330–332
Integrase (IN) protein, 59–71
discovery of, 60
prototype foamy virus, 63–65
role in integration site targeting, 68
roles in HIV biology, 71
structural studies of, 63–65
in vitro integration assays using purified integrase, 62
Integration, 59–71
biochemical studies of mechanism, 60–65
preintegration complex (PIC), 61, 62
similarities to DNA transposition, 62–63
structural studies of integrase, 63–65
in vitro assays using purified integrase, 62
cellular context, 65–71
DNA breaking and joining reactions, 61
fates of viral DNA in the nucleus, 66
host factors and, 70–71
LEDGF/p75 role in, 69–70
microbicides targeting, 514

Index

- Integration (*Continued*)
nuclear localization, 65–66
overview, 59–60
target site selection, 66–69
tethering model, 70
- Integrin $\alpha 4\beta 7$, 29–30
- Interferon, production by dendritic cells, 256
- Intrabodies and intrakines, 347–348
- Intravaginal rings, 505, 515
- Intrinsic immune response, to primate lentivirus infection, 470
- origins and phylogeny, 306–308
recombination, 308–309
phylogeny of, 3
“viral fossils,” 4
- Linkage, effect on evolution, 186
- Lipid composition, viral, 99
- Liver, pathogenesis in, 169
- LTR (long terminal repeat), as viral promoter, 77–78, 81–82
- Lung, pathogenesis in, 169
- Lymph nodes, dissemination and persistence in, 167
- ### K
- Kidney, pathogenesis in, 169
- Killer immunoglobulin-like receptors (KIRs)
as driver of viral evolution, 262–263
groups, 259
KIR3DL1-mediated control of HIV, 261, 262
KIR3DS1-mediated control of HIV, 259–261
NK cell recognition of HIV-infected target cell, 257, 258
role in modulating HIV disease progression, 259
two-domain KIRs, 261–262
tyrosine-based activation motifs, 259
tyrosine-based inhibition motifs, 259
- ### L
- Late domains, 103–104
- Latency, 267–280
clinical significance of, 276–278
definitions, 267–268
eradication strategies and, 279–280, 351–352
history, 267–270
molecular mechanisms of, 270–276
chromatin, 270–272
DNA methylation, 272
RNA Pol II elongation, 275–276
RNA Pol II initiation, 274–275
RNA splicing and export, 276
transcriptional interference, 273–274
reservoirs for, 278–279
- Latin America, epidemic trends in, 371–372
- Lattice, immature, 101–103
- LEDGF/p75, role in integration, 69–70
- Lemurs, lentiviruses of, 4
- Lentiviruses
endogenous transmission, 4
evolution, 4–5
exogenous transmission, 3–4
nonpathogenic simian immunodeficiency viruses (SIVs)
cross-species transmission, 308–309
epidemiology, 308–309
- ### M
- Macaques
disease in Asian, 463–464
genetic studies, 417
primate-SIV infection transmission model, 147–150
SHIV infection of rhesus, 473–474
- Macrophages
latency in, 279
as target cell, 163–164
- MACS (Multicenter AIDS Cohort Study), 179
- Male circumcision, 547–549
biological reasons for protection, 547, 549
clinical trials, 547–549
implementation programs, 549
- Maraviroc, 512
- Mathematical models of HIV transmission, 147
- Maturation
architecture of mature virion, 106
capsid, 106–108
dynamics of, 109
microbicides targeting, 514–515
protease, 108–109
- Membrane
models of membrane fission, 105–106
viral lipid composition, 99
- Membrane bridges, 111
- Membrane fission, models of, 105–106
- Memory CD4⁺ T cells, HIV-1 latency in, 267–280
- Men who have sex with men, as risk exposure, 392–395
- MHC class I
down-regulation of, 257–258
killer immunoglobulin-like receptors (KIRs) and, 257, 258
- MHC locus in primate models, 417–418
- Microbial translocation, 203–205
chronic immune activation and, 313
lack of, 314–315
- Microbicides, 505–519
ARV drugs to prevent initial events in mucosal transmission, 507–511
combination, 518

- in context of other prevention technologies, 518–519
 - development
 - early history, 506–507
 - formulation strategies, 515–516
 - new research areas, 515–516
 - principles for prioritizing, 506
 - dosing schemes, 516
 - efficacy, 506
 - inhibition of coreceptor interaction, 511–512
 - matching to mechanisms of transmission, 507
 - pharmacokinetics and pharmacodynamics, 516–517
 - resistance to ARV-based, 517–518
 - safety, 506
 - targeting of viral entry, 511
 - targeting reverse transcriptase, 512–514
 - NNRTIs (nonnucleoside reverse transcriptase inhibitors), 513–514
 - NRTIs (nucleoside reverse transcriptase inhibitors), 512–513
 - targeting viral integration, 514
 - targeting viral maturation, 514–515
- Microglia, 290
- “Missing self” model of NK recognition, 257
- Modified Vaccinia Ankara, 490–492
- Molecular clock, 4, 10
- Molecular epidemiology, 372–376, 391–392
- Monoclonal antibodies, identification and characterization of, 225
- Monocytes
 - central nervous system entry, 279
 - infection of, 279
 - as target cell, 163
- Mother-to-child transmission, 223–224, 398, 515
- mRNA
 - alternative splicing, 82–84
 - guiding of transcripts through the cytoplasm, 87
 - nuclear retention of mRNAs, 87
 - processing and polyadenylation, 87–88
 - RNA export, control of, 84–87
 - translation initiation, 88
- Mucosal immune system
 - antiretroviral therapy and, 201–202
 - general features of, 196–197
 - immunophenotypic composition of, 197–198
 - interactions with intestinal structure and function, 198
- Mucosal tissues
 - HIV infection and mucosal immune system, 196–198
 - microbial translocation, 203–205
- Mucosal transmission
 - antiretroviral drugs to prevent initial events in, 507–511
 - in nonhuman primates, 465, 467
- Multicenter AIDS Cohort Study (MACS), 179
- Mutation
 - APOBEC3G (A3G) and, 123–124
 - HIV-1 evolution, 184–185
- Myristoyl switch model, 98
- N**
- Nanotubes, membrane, 111
- Nef
 - HIV evasion of NK cells through, 257–258
 - tetherin antagonism by, 129
 - tetherin interaction in SIVs, 13
- Nervous system. *See also* Central nervous system (CNS)
 - HIV-associated neurocognitive disorders (HAND), 288, 292–295, 297, 298
 - viral entry and maintenance of infection in, 288–291
- Neuropathogenesis, strain-specific, 292–293
- Neutralizing antibodies
 - development of broadly cross-neutralizing antibodies, 219–222
 - response against HIV-1, 217–227
 - role in protection, 448–449
 - vaccine design to elicit, 447–458
- Nevirapine, and prevention of mother-to-child transmission, 515
- Next-generation sequencing, 421–422
- NK cells
 - HIV evasion through Nef, 257–258
 - killer immunoglobulin-like receptors (KIRs)
 - as driver of viral evolution, 262–263
 - groups, 259
 - KIR3DL1-mediated control of HIV, 261, 262
 - KIR3DS1-mediated control of HIV, 259–261
 - NK cell recognition of HIV-infected target cell, 257, 258
 - role in modulating HIV disease progression, 259
 - two-domain KIRs, 261–262
 - “missing self” model of recognition, 257
 - overview of, 257
 - as target cell, 164
 - two-step activation model, 260

NKG2D receptor, 258

NNRTIs. *See* Nonnucleoside reverse transcriptase inhibitors

Nonhuman primate models
 - immune responses, 470–475
 - B-cell responses, 471–472
 - immune responses, 470–471
 - T-cell responses, 472, 474–475
 - modeling vaccine development, 463–475, 486

Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
 - mode of action, 514
 - overview, 329–330, 513–514
 - resistance, 51, 329–330
 - structure, 329

Index

- Nonsyncytium-inducing viruses, 161
- North America, viral diversity in, 388
- NRTIs. *See* Nucleoside reverse transcriptase inhibitors
- Nucleic acid-based inhibitors, 348–350
 - antisense RNA, 348–349
 - aptamers, 349
 - ribozymes, 349–350
 - RNA decoys, 349
 - RNA interference, 350
- Nucleoside reverse transcriptase inhibitors (NRTIs)
 - mode of action, 327, 513
 - overview, 327–328, 512–513
 - resistance mechanisms, 327, 328
 - resistance mutations, 51, 327–328
 - structure, 51, 328
- Nucleus
 - fates of viral DNA in, 66
 - HIV localization in, 65–66
- Nup358, 66

- O**
- Oral preexposure prophylaxis, 523–533
- Origins of HIV, 1–16
 - AIDS pandemic, 1–2, 14–15
 - HIV-1 origins, 8–11
 - HIV-2 origins, 11, 12
 - host-specific adaptations, 11–14
 - overview, 1–3
 - primate lentiviruses, 3–5
 - SIV_{cpz}
 - natural history of infection, 7–8
 - origin and distribution, 5–7
 - SIV_{gor}, origin and distribution, 8

- P**
- Pacific Rim, epidemic spread of HIV to, 374–376
- Paleovirology, 422
- Pathogenesis
 - AIDS, 188–189
 - dissemination and persistence in target tissues, 164–170
 - dynamics and genetics of viral populations and infected cells, 177–190
 - genetic variation and evolution, 184–188
 - HIV-1 steady state, 181–184
 - implications, 181
 - nature and lifetimes of infected cells, 181–182
 - persistence of infection on therapy, 182
 - host and, 193–207
 - cellular targets for SIV/HIV, 196
 - clinical manifestations of infection, 194–195
 - early immune response, 200–201
 - early targets of infection, 198–199
 - key aspects, 195–196
 - microbial translocation, 203–205
 - mucosal tissues, 196–198
 - role of immune activation in disease pathogenesis, 202–203
 - role of inflammation/activation in complications of treated infection, 205–207
 - systemic lymphoid tissues, 199–200
 - in low- to middle-income countries, 376–377
 - studies in animal models, 309–313
 - target cells, 162–164
 - monocytes, macrophages, and NK cells, 163–164
 - T-cell subsets, 162–163
 - time course of HIV-1 infection, 164, 177–179
 - viremia, significance of, 179–180
 - virus and, 159–170
 - dissemination and persistence in target tissues, 164–170
 - mechanisms of cell killing, 170
 - overview, 159–160
 - target cells, 162–164
 - transmission, 160–162
- Pattern recognition receptors, 255
- Peptide vaccine trials, 488
- Pharmacodynamics, microbicide, 516–517
- Pharmacokinetics, microbicide, 516–517
- Phylogenetic modeling, 391–392
- Phylogeny of lentiviruses, 3, 306–308
- Plasma membrane, HIV-1 assembly and budding at, 109
- Polypyrimidine tract binding protein (PTB), 276
- Population bottleneck to HIV-1 transmission, 140–144
- Pox virus vectors, 434–435, 436, 490–494
- PR (viral protease)
 - action of, 108–109
 - structure, 108
- Predominant plasma clones, 184
- Preexposure prophylaxis (PrEP)
 - microbicides, 505–519
 - oral, 523–533
 - antiretroviral drugs, 524–528
 - human clinical trials, 531–533
 - preclinical research in animal models, 528–531
- PrEP. *See* Preexposure prophylaxis
- Prevention
 - among injecting drug users, 550–553
 - challenges and opportunities for implementation, 553
 - evidence for efficacy, 552–553
 - structural interventions, 552
 - behavioral and biomedical strategies, 537–555
 - behavioral, 539–542
 - overview, 537–538
 - counseling and testing, 544
 - male circumcision, 547
 - microbicides, 505–519
 - oral preexposure prophylaxis, 523–533
 - with positives, 544–547

- clinical research in discordant couples, 545
- evidence for reduced transmission, 545
- mathematical models, 546–547
- research, 545
- STI interventions, 550
- structural approaches, 553–554
 - design and evaluation, 554
 - evidence for link to HIV, 553
 - examples, 553–554
- topical, 505–519
- vaccines
 - design for CD8 T lymphocyte responses, 431–440
 - lessons in nonhuman primate models for research, 463–475
 - rational design to elicit neutralizing antibodies, 447–458
 - trials, 483–496
- Primates. *See also* Simian immunodeficiency viruses (SIVs)
 - genetics, 416–420
 - chemokine receptors and chemokines, 420
 - macaques, 417
 - MHC locus in primate models, 417–418
 - restriction factors, 418–420
 - models for oral preexposure prophylaxis, 528–531
 - nonhuman primate models, 463–475, 486
- Protease inhibitors
 - as microbicides, 514–515
 - overview, 332, 333
 - structure, 333
- Protein-based inhibitors, 347–348
 - dominant negative inhibitory proteins, 347
 - fusion inhibitors, 348
 - intrabodies and intrakines, 347–348
 - of TRIM5 α , 348
- Protein reconstruction, 422
- Protein trafficking and virion incorporation, 98–99
- Proto-oncogenes, insertional activation of, 70
- Prototype foamy virus, 63–65
- Provirus
 - chromatin compaction around, 271
 - HIV-1 latency in CD4⁺ T cells, 267–280
- P-TEFb
 - as cofactor for Tat, 79–80
 - regulation of, 81
- R**
- Rabbit endogenous lentivirus type k (RELK), 4
- Recombination
 - models, 50
 - reverse transcription and, 48–51
- Recombination, in simian immunodeficiency viruses (SIVs), 308–309
- Reservoirs, 278–279
- Restriction factors, 119–131
 - APOBEC3 proteins, 121–125
 - as barriers to SIV cross-species transmission, 13–14
 - cardinal and shared features of, 121
 - discovery of, 120–121
 - evolution of, 13
 - mechanisms of function, 123
 - new research areas, 130–131
 - overview, 119–120
 - primate, 418–420
 - tetherin, 127–130
 - TRIM5 α and TRIMCYP, 125–127
- Retroviruses. *See also* Lentiviruses
 - human endogenous retroviruses (HERV), 438
 - insertional activation of proto-oncogenes, 70
 - integration target sites, 68
 - recombination, 48–51
- Reverse transcriptase
 - antivirals targeting, 51
 - discovery of, 37, 60
 - enzymatic functions of, 44
 - errors made by, 14, 46–48
 - microbicides targeting, 512–514
 - NNRTIs (nucleoside reverse transcriptase inhibitors), 513–514
 - NRTIs (nucleoside reverse transcriptase inhibitors), 512–513
 - production of, 40–41
 - structure of, 41–44
- Reverse transcriptase inhibitors
 - nonnucleoside reverse transcriptase inhibitors (NNRTIs)
 - mode of action, 514
 - overview, 329–330, 513–514
 - resistance, 51, 329–330
 - structure, 329
 - nucleoside reverse transcriptase inhibitors (NRTIs)
 - mode of action, 327, 513
 - overview, 327–328, 512–513
 - resistance mechanisms, 327, 328
 - resistance mutations, 51, 327–328
 - structure, 51, 328
- Reverse transcription, 37–51
 - avian sarcoma-leukosis virus (ASLV), 40
 - in infected cells, 44–46
 - mutations and fidelity, 46–48
 - overview, 37–38
 - process of, 38–40
 - recombination, 48–51
 - RNase H and, 38–40
- Reverse transcription complex, 44–45
- Rev protein
 - control of RNA export, 84–87
 - M10 mutant, 347
 - RRE interactions, 86
- Rev-responsive element (RRE), 84–87

Index

- Rhesus macaques, SHIV infection of, 473–474
Ribozymes, 349–350
Risk exposures, 392–398
 blood/blood product administration, 396–397
 heterosexual spread, 397–398
 iatrogenic exposure, 396–397
 injection drug use, 395–396
 men who have sex with men, 392–395
 mother-to-child transmission, 398
RNA. *See also* mRNA
 antisense RNA, 348–349
 decoy, 349
 packaging, 96–98
 splicing and export, HIV-1 latency and, 276
 trafficking and incorporation, 99–101
RNA aptamers, 349
RNA decoys, 349
RNA export
 control of, 84–87
 HIV-1 latency and, 276
RNA interference (RNAi), 350
RNA Pol II
 errors made by, 46–48
 HIV-1 latency
 RNA Pol II elongation and, 275–276
 RNA Pol II initiation and, 274–275
RNase H, 38–40, 63
RRE (Rev-responsive element), 84–87
RV144, 494–495
- S**
- SAMHD1, 130
Sequencing, next-generation, 421–422
Sexually transmitted infections (STIs), 550
Signal transduction, viral entry and, 30–32
 CCR5 and CXCR4, 31–32
 CD4, 30–31
 HIV Env, 30
Simian-human immunodeficiency virus (SHIV), 448,
 464, 467–469, 471–473
Simian immunodeficiency viruses (SIVs)
 cellular targets for, 196
 chronic immune activation
 attenuated, 313–314
 microbial translocation and, 313
 pathogenesis studies, 313
 cross-species transmission, 2, 4, 308–309
 discovery of, 2
 early targets of infection, 198–199
 HIV-1 origins, 8–11
 HIV-2 origins, 11, 12
 host species, 307
 host-specific adaptations, 11–14
 lineages, 308
 microbial translocation
 chronic immune activation and, 313
 lack of, 314–315
 nonpathogenic infections, 305–316
 cross-species transmission, 308–309
 epidemiology, 308–309
 mechanisms, 313–315
 origins and phylogeny, 306–308
 recombination, 308–309
 target cell restriction, 315
 pathogenesis studies in animal models, 309–313
 adaptive immune responses, 312
 characteristics of natural infections, 309–311
 chronic immune activation and microbial
 translocation, 313
 experimental animal models, 309
 innate immune responses, 312–313
 target cells for SIV replication, 311–312
 phylogeny of lentiviruses, 3
 prevalence of infection, 4
 primate-SIV infection transmission model,
 147–150
 role of immune activation in disease pathogenesis,
 202–203
SIVcpz
 HIV-1 origins and, 8–11
 natural history of infection, 7–8
 origin and distribution, 5–7
SIVgor, origin and distribution, 6, 8
SIVmm, 11
 tetherin antagonists, 129–130
Sooty mangabey, 11, 305–315
South America
 epidemic spread of HIV to, 374
 HIV/AIDS statistics, 370
 HIV prevalence, 369
Splicing
 alternative splicing of HIV-1 mRNA, 82–84
 HIV-1 latency and, 276
STIs (sexually transmitted infections), 550
Systems biology, 423
- T**
- Target cells, 162–164
 macrophages, 163–164
 monocytes, 163
 NK cells, 164
 for SIV replication, 311–312
 T-cell subsets, 162–163
Target tissues
 blood and lymph nodes, 166–167
 breast, 170
 CNS, 167–168
 dissemination and persistence in, 164–170
 early targets of infection, 198–199
 genital tract, 168

- gut-associated lymphoid tissue (GALT), 167
- hematopoietic stem cells, 169–170
- kidney, 169
- liver, 169
- lung, 169
- TAR RNA, Tat interaction with, 79
- Tat
 - HIV latency and, 274–276
 - transcription control by, 77–82
 - discovery of transactivation by Tat, 77–79
 - epigenetic regulation, 82
 - LTR as a promoter, 81–82
 - P-TEFb, regulation of, 81
 - P-TEFb as cofactor for Tat, 79–80
 - Tat/TAR RNA interaction, 79
 - transactivation mechanism, 80–81
 - transcriptional feedback, 82
- T-cell response, 235–247
 - CD4⁺ T-cell responses, 239–240
 - CD8⁺ T cell functions in HIV infection, 245–246
 - cytotoxic T lymphocyte (CTL)
 - evolution following acute infection, 238–239
 - immune pressure and viral escape, 240–242
 - responses in acute infection, 236–238
 - immunogenetics of HIV-specific, 242–245
 - in nonhuman primates, 472, 474–475
 - overview, 235–236
- T cells. *See also specific T cell types*
 - characteristics associated with virus control, 432–433
 - response of, 235–247
 - vaccine design for response, 431–440
- Temin, Howard, 37, 60
- Tenofovir
 - dosing, 515
 - mode of action, 513
- Tetherin, 127–130
 - antagonism by Vpu, Nef, and Env proteins, 129
 - as barrier to SIV cross-species transmission, 13–14
 - block to HIV-1 release, 106
 - domain organization, 122
 - evolution of, 13, 30
 - identification, 127
 - mechanism of virion retention, 128–129
 - SIV antagonists, 129–130
 - structure, 13, 128–129
- Time course of HIV-1 infection, 164, 177–179
- Topical prevention, 505–519
- Transactivation
 - discovery of transactivation by Tat, 77–79
 - mechanism, 80–81
- Transcriptional feedback, control of HIV-1 replication by, 82
- Transcriptional interference, HIV-1 latency and, 273–274
- Transcription control by Tat, 77–82
 - discovery of transactivation by Tat, 77–79
 - epigenetic regulation, 82
 - LTR as a promoter, 81–82
 - P-TEFb, regulation of, 81
 - P-TEFb as cofactor for Tat, 79–80
 - Tat/TAR RNA interaction, 79
 - transactivation mechanism, 80–81
 - transcriptional feedback, 82
- Translation
 - frameshifting, 88
 - initiation, 88
- Transmission, 135–151. *See also* Prevention
 - antibodies and, 223–225
 - ARV drugs to prevent initial events in mucosal transmission, 507–511
 - cell-to-cell, 110, 111
 - clinical event and acute infection, 138–140
 - drug-resistant HIV, 390–392
 - early events in replication, 161–162
 - early targets of infection, 198–199
 - epidemiological implications for, 135–136
 - founder virus, nature of, 161
 - frequency and mechanism, 160–161
 - genetic signatures and phenotypes of transmitted/founder viruses, 144–146
 - in high-income countries, 390–392
 - microbicide matching to mechanisms of, 507
 - models, 142, 147–151
 - of cervicovaginal infection, 148
 - human tissue explant, 150–151
 - mathematical, 147
 - primate-SIV infection, 147–150
 - modulating factors, 138
 - mother-to-child, 223–224, 398, 515
 - pathogenesis and, 160–162
 - population bottleneck to, 140–144
 - risk exposures, 392–398
 - blood/blood product administration, 396–397
 - heterosexual spread, 397–398
 - iatrogenic exposure, 396–397
 - injection drug use, 395–396
 - men who have sex with men, 392–395
 - mother-to-child transmission, 398
 - routes and risks for HIV-1, 136–138
 - simian immunodeficiency viruses (SIVs)
 - cross-species transmission, 2, 4, 308–309
 - viral load and, 138, 545, 546
- Transmitted/founder (T/F) virus, 486
- Transplantation, allogeneic and xenogeneic, 346–347
- Transportin 3, 66
- Transposition, integration similarity to, 62–63
- Treatment. *See also* Antiretroviral therapy (ART); Prevention
 - latency and, 276–280
 - novel therapies, 345–360

Index

- Treatment. *See also* Antiretroviral therapy (ART);
Prevention (*Continued*)
allogeneic and xenogeneic transplantation,
346–347
CCR5 as target, 350–355
clinical trials, 355, 356–359
gene-editing strategies, 352–355
gene therapy, 352
nucleic acid-based inhibitors, 348–350
protein-based inhibitors, 347–348
sexually transmitted infections (STIs), 550
- Trials
behavioral strategies for prevention, 541–542
male circumcision, 547–549
oral preexposure prophylaxis (PrEP), 531–533
STI treatment, 550, 551
vaccine, 435, 449, 483–496
adenoviral vector, 488–490
DNA prime protein subunit boost, 487–488
modeling vaccine development, 484–486
in nonhuman primates, 466
peptide, 488
protein subunit alone, 486–487
- TRIM5 α , 125–127
action, 126
domain organization, 122
identification, 125
inhibitors of, 348
mechanisms of infection inhibition by, 126–127
structure, 125–126
- TRIMCYP, 126–127
- U**
- United Kingdom, phylodynamic modeling and,
391–392
- V**
- Vaccine
breadth of, 438–439
challenges for, 483–484
completed phase II and III, 485
consequences of genetic diversity on development,
378–379
design for CD8 T lymphocyte responses, 431–440
antigens targeted, 436–438
breadth of recognition, 438–439
epitope escape, 439
location of response, 438
design to elicit neutralizing antibodies, 447–458
adjuvants, 458
clinical trials, 449
humoral immune response and, 450
immunogen design, 455–458
sites of HIV-1 vulnerability, 451–455
structural virology, 450–451
- DNA, 433–434, 487–488
general approaches to development, 484
genomics, 413–414
immunogen design, 455–458
B-cell biology and, 457–458
CD4bs immunogens, 455, 456
CD4i region, 457
glycan and quaternary immunogens, 455–457
MPER region, 457
V3 region, 457
modalities and immunity elicited, 433
modeling vaccine development, 484–486
acute infection, 486
nonhuman primate models, 463–475, 486
product development pathway, 494–496
trials, 435, 449, 483–496
adenoviral vector, 488–490
DNA prime protein subunit boost, 487–488
modeling vaccine development, 484–486
in nonhuman primates, 466
peptide, 488
protein subunit alone, 486–487
viral vectors, 434–436, 488–494
Vaccinia virus vectors, 434, 449, 490–492
Vectors, viral, 434–436, 488–494
- Vif
APOBEC3 proteins and, 121–125
inhibition of A3G function, 123–124
- Viral diversity in Northern Hemisphere, 388–390
Europe 1980–1990, 388–390
Europe 1990–2005, 390
North America, 388
- Viral escape, early antibodies and, 218–219
- Viral load
relationship to clinical progression, 179
transmission risk and, 138, 545, 546
- Viral vectors, 434–436, 488–494
- Viremia
decay of circulating virus, 180–181
significance of, 179–180
- Virions
architecture of mature, 106
assembly, budding, and maturation, 95–111
capsid, 106–108
- Virological synapse, 109–111
- Vpu protein
tetherin antagonism by, 129
tetherin interaction in SIVs, 13
- X**
- Xenogeneic transplantation, 346
- Z**
- Zinc finger nucleases, 347, 353–355