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
eyearly 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
CCR5Δ32 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
genotype 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

© 2011 by Cold Spring Harbor Laboratory Press
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 of 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

© 2011 by Cold Spring Harbor Laboratory Press
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
ESCRRT (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 1990–2005, 390
North America, 388
“viral fossils,” 4
Evolutionary genomics, 422
Frameshifting, 88
Fullerene cone model for HIV-1 capsid, 106–108
Fusion inhibitors, 332, 335, 348
G
Gag polyprotein
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 (GWAS), 410–413
Genomics, 410–416
advanced genome analyses, 414–416
data integration, network, and systems biology, 423
evolutionary, 422
genome-wide association studies (GWAS), 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
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
ESCRRT (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 1990–2005, 390
North America, 388
“viral fossils,” 4
Evolutionary genomics, 422
Frameshifting, 88
Fullerene cone model for HIV-1 capsid, 106–108
Fusion inhibitors, 332, 335, 348
G
Gag polyprotein
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 (GWAS), 410–413
Genomics, 410–416
advanced genome analyses, 414–416
data integration, network, and systems biology, 423
evolutionary, 422
genome-wide association studies (GWAS), 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

F
FDA drug approval, timeline for, 322
Female condom, 543
Founder virus, 161
Gut-associated lymphoid tissue (GALT), dissemination and persistence in, 167
GWASs (genome-wide association studies), 410–413

H

© 2011 by Cold Spring Harbor Laboratory Press
Index

Integration (Continued)
nuclear localization, 65–66
overview, 59–60
target site selection, 66–69
tethering model, 70
Integrin α4β7, 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

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
LEDF/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
origin 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

M
Macques
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

© 2011 by Cold Spring Harbor Laboratory Press
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

© 2011 by Cold Spring Harbor Laboratory Press
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
- SIVcpz
  - natural history of infection, 7–8
  - origin and distribution, 5–7
- SIVgor, 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
- Phylodynamic 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

© 2011 by Cold Spring Harbor Laboratory Press
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

elements, 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 TRIM5α, 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-TEFβ

as cofactor for Tat, 79–80

regulation of, 81

R

Rabbit endogenous lentivirus type k (RELIK), 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

TRIM5α 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 (nonnucleoside 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

© 2011 by Cold Spring Harbor Laboratory Press

569
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
   SIVsmm, 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

© 2011 by Cold Spring Harbor Laboratory Press
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
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
eye events in replication, 161–162
eye 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
TRIM5α, 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, phylogenetic 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 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