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HIV—Disease Overview, Targets for Therapy and Open Issues

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Nearly 40 years have passed since the first patients were discovered to have the previously unknown "acquired immunodeficiency syndrome" (AIDS) [1] and 38 years, since the causative virus was discovered [2]. The time since, has been characterized by a dynamically evolving body of epidemiological and basic science that is unique in medical history. Preliminary result is the development of antiretroviral treatments and social medicine progress, accompanied and catalyzed by the predominantly affected risk groups' emancipation, with reintegration into the society.

1.1 HIV—Disease Overview

There has not been a significant change in the **natural history of HIV-infection**; however, today in industrialized countries, disease manifestation in the form of AIDS can only be observed in undiagnosed, late presenting patients, who already show manifestations of immunological deterioration. Figure 1.1 demonstrates the course of the disease, according to the two most important measurable surrogate markers—CD4-cell count and HIV-RNA (viral load).

After initial HIV transmission, the retrovirus spreads throughout the human body and infects potentially all CD4-receptor positive cells. Consequently, during the first weeks of infection, there is a substantial fall in CD4-positive T-lymphocyte count and a rise in viral load—up to a turning point. Thereafter, CD4-cells rise again and viral load decreases, due to regain of a partial immunological control. At this time, anti-HIV antibodies can be found in plasma, and the patient will now respond positively to serological HIV-tests. Elimination of HIV, however, will not occur due to the rapid variation of viral surface receptors which may hide infected cells from the immune system and lead to divergent virus populations, including in a single patient [3, 4, 5, 6]. This continuous change of HIV stems from proofreading failures which lead to the evolution of many

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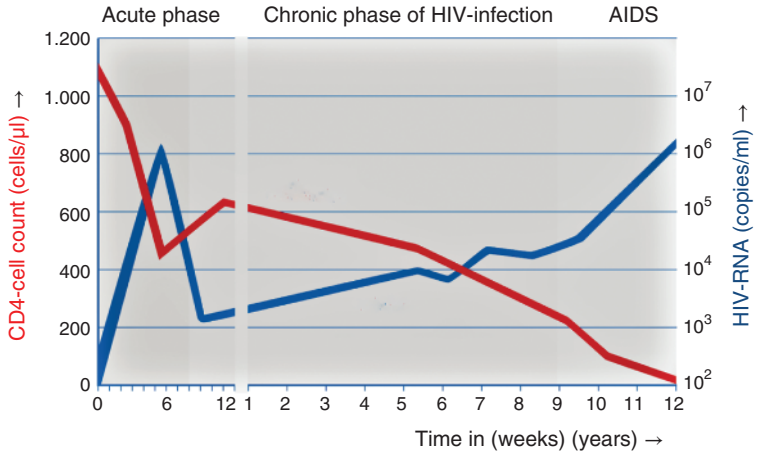


Figure 1.1 Shows the course of both most important measurable surrogate markers from blood count, i.e. CD4-cell count and HIV-RNA (viral load), during untreated HIV infection.

HIV quasispecies. Another reason for the inability to eliminate HIV is the infection of durable reservoir and "archive" cells, e.g. edaphic CD4-receptor-positive macrophage and monocyte cells, leading to the chronic phase of the infection. For approximately 3–10 years, the patient will experience a relatively stable period, marked by individually solid CD4-cell count- and HIV-RNA viral load- "setpoints" [7]. However, after months or years, an immunological exhaustion will occur. Then, the CD4-cell count is substantially decreasing and viral load is rising again. The result may be AIDS, as defined by the emergence of at least one of 26 opportunistic infections and/or tumors, including pneumocystis pneumonia, cerebral toxoplasmosis, tuberculosis, cytomegalovirus retinitis, Kaposi's sarcoma, or B-cell non-Hodgkin lymphoma.

1.2 Targets for Antiretroviral Therapy

The replication of the retrovirus in the human host cell is well described and offers targeted treatment options, in order to prevent viral replication. Figure 1.2 shows the passage of HIV through the human host CD4-receptor positive T-cell. Antiretroviral drugs are able to address specific points in the HIV replication cycle and used in combination antiretroviral therapy (cART) aims to completely suppress HIV-1 replication long term. This will give the immune system a chance to recover and overcome opportunistic infections and tumors and/or to avoid significant deterioration from the beginning, when applied early after infection.

During the retrovirus replication in the human cell, specific cART-drug classes offer to interfere with different therapeutic intervention targets (see Table 1.1, presently favored drugs are printed in bold and Figure 1.2). Such interventions comprise: inhibition of first contact of HIV with the CD4-positive cell (attachment), the cell entry, intracellular reverse

transcriptase-enzyme and -activity, DNA-integration, virus assembling by proteases, and virus maturation; the latter leaves immature, noninfectious virus particles. The chemical structures of the different HIV drugs can be found in Table 1.2.

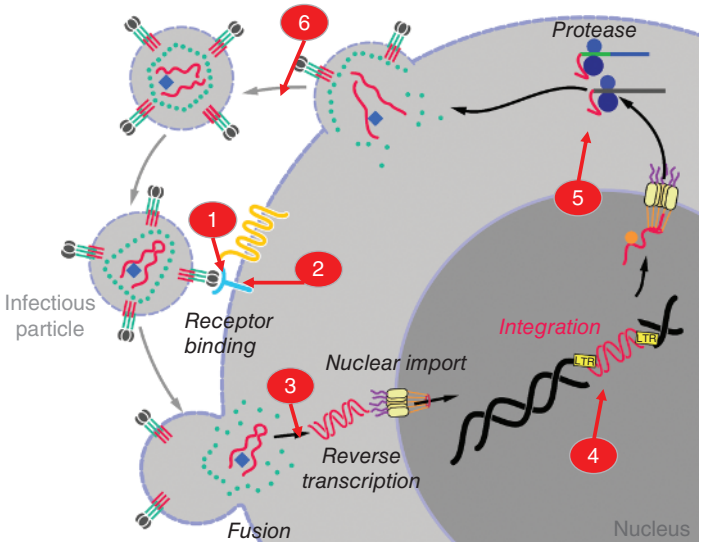


Figure 1.2 Shows the viral replication cycle for HIV in the human target cell, i.e. the CD4-receptor positive cell, and six treatment targets for antiretroviral therapy classes (for numbers in red, see Table 1.1/row 1).

Table 1.1 Explains the mode of action for available cART options, according to the target area in HIV cell passage (for numbers: see Figure 1.2).

No. (Figure 1.2)	Drug class: inhibitor of…	Generic names of available cART-drugs	Mode of action: inhibition of the…	Formula	CAS registry number
1	Attachment	Fostemsavir[a]	HIV-binding site gp120, used by HIV for first contact with CD4-receptor	$C_{25}H_{26}N_7O_8P$	864953-29-7
		Ibalizumab (TNX-355)	Human CD4-receptor binding site for HIV (whole antibody)	n/a	680188-33-4
2	Entry-/fusion	Enfuvirtid (T20)	HIV-gp41-fusion protein (36 amino acids-containing polypeptide)	$C_{204}H_{301}N_{51}O_{64}$	159519-65-0
		Maraviroc (MVC)	Human CCR5-coreceptor	$C_{29}H_{41}F_2N_5O$	376348-65-1

(Continued)

Table 1.1 (Continued)

No. (Figure 1.2)	Drug class: inhibitor of…	Generic names of available cART-drugs	Mode of action: inhibition of the…		Formula	CAS registry number
3	Nucleosidal reverse transcriptase (NRTI)	Zidovudin (AZT)	Thymidin-analogue	Nucleobase replacement during RNA–DNA-transcription as faulty chip, leading to early chain termination	$C_{10}H_{13}N_5O_4$	30516-87-1
		Lamivudin (3TC)[b]	Cytidin-analogue		$C_8H_{11}N_3O_3S$	134678-17-4
		Emtricitabine (FTC)[b]			$C_8H_{10}FN_3O_3S$	143491-57-0
		Tenofovir (TAF/TDF)[b]	Adenosine-analogue		$C_9H_{14}N_5O_4P$	147127-20-6
		Abacavir (ABC)[b]	Gunaosine-analogue		$C_{14}H_{18}N_6O$	136470-78-5
4	Non-nucleosidal reverse transcriptase (NNRTI)	Efavirenz (EFV)	Reverse transcriptase-enzyme binding site		$C_{14}H_9ClF_3NO_2$	154598-52-4
		Nevirapine (NVP)			$C_{15}H_{14}N_4O$	129618-40-2
		Rilpivirine (RPV)[b]			$C_{22}H_{18}N_6$	500287-72-9
		Doravirin (DOR)[b?>]			$C_{17}H_{11}ClF_3N_5O_3$	1338225-97-0
5	Integrase strand transfer (INSTI)	Raltegravir (RGV)	Viral DNA integration in human host DNA, in cell nucleus		$C_{20}H_{21}FN_6O_5$	518048-05-0
		Elvitegravir (EVG)			$C_{23}H_{23}ClFNO_5$	697761-98-1
		Dolutegravir (DGT)[b]			$C_{20}H_{19}F_2N_3O_5$	1051375-16-6
		Bictegravir (BTG)[b]			$C_{21}H_{18}F_3N_3O_5$	1611493-60-7
		Cabotegravir[a]			$C_{19}H_{17}F_2N_3O_5$	1051375-10-0
6	Protease (PI)	**Darunavir (DRV)**[b]	gag-pol-polyprotein cleavage		$C_{27}H_{37}N_3O_7S$	206361-99-1
		Atazanavir (ATV)			$C_{38}H_{52}N_6O_7$	198904-31-3
		Lopinavir (LPV)			$C_{37}H_{48}N_4O_5$	192725-17-0
7	Maturation/capsid	Lenacapavir[a]	Extracellular capsid arrangement[a]		$C_{39}H_{32}ClF_{10}N_7O_5S_2$	2189684-44-2
		GSK3640254[a]	Last protease cleavage event: CA-p24/SP1[a]		n/a	n/a

a) In clinical study development—also refer to public study registry online-resource, available at: https://www.clinicaltrials.gov.

b) Modern, recommended first-line combination antiretroviral therapy components: printed in **bold**. For treatment guidelines from the European AIDS Clinical Society (EACS), version 10, from November 2019, please refer to online-resource, available at: https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf.

Table 1.2 Illustrates chemical formula details and CAS registry numbers for available cART-drugs.

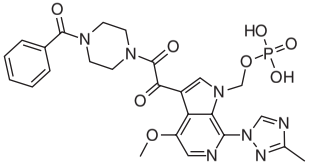
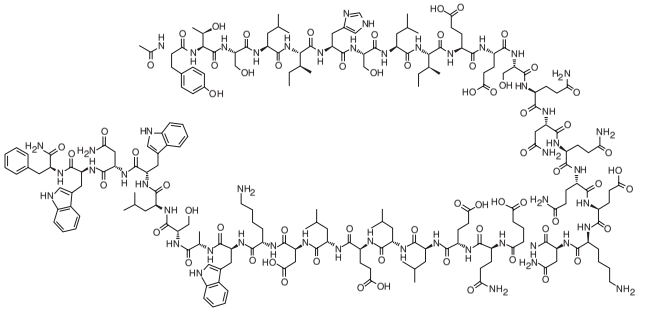
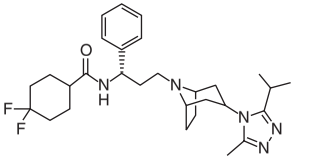
Drug class: inhibitor of…	Generic drug name/chemical formula/CAS registry no./graphic structure formula	Generic drug name/chemical formula/CAS registry no./graphic structure formula
Attachment	Fostemsavir[a] $C_{25}H_{26}N_7O_8P$ 864953-29-7 	Ibalizumab (TNX-355) n/a 680188-33-4 n/a—chemical formula not yet published, the drug is a humanized mouse whole antibody
Entry-/fusion	Enfuvirtid (T20) $C_{204}H_{301}N_{51}O_{64}$ 159519-65-0 	Maraviroc (MVC) $C_{29}H_{41}F_2N_5O$ 376348-65-1 

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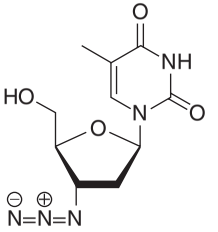
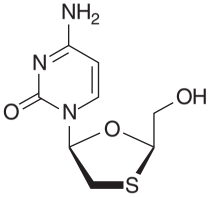
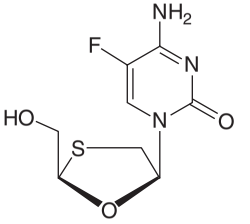
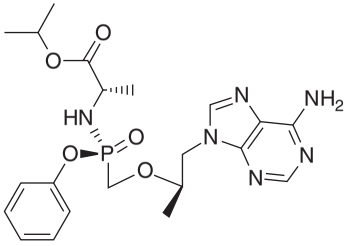
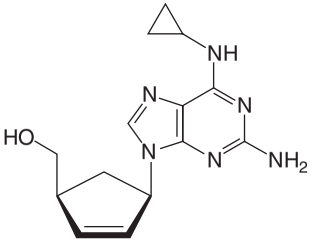
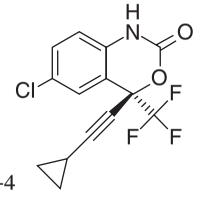
Table 1.2 (Continued)

Drug class: inhibitor of...	Generic drug name/chemical formula/CAS registry no./graphic structure formula	Generic drug name/chemical formula/CAS registry no./graphic structure formula	
Nucleosidal reverse transcriptase (NRTI)	Zidovudin (AZT) Thymidin-analogue $C_{10}H_{13}N_5O_4$ 30516-87-1 	Lamivudin (3TC) Cytidine-analogue $C_8H_{11}N_3O_3S$ 134678-17-4 	Emtricitabine (FTC) Cytidine-analogue $C_8H_{10}FN_3O_3S$ 143491-57-0 
	Tenofovir (TAF/TDF) Adenosine-analogue $C_9H_{14}N_5O_4P$ 147127-20-6 As tenofovir alafenamid (TAF) 	Abacavir (ABC) Guanosine-analogue $C_{14}H_{18}N_6O$ 136470-78-5 	

Non-nucleosidal reverse transcriptase (NNRTI)

Efavirenz (EFV)

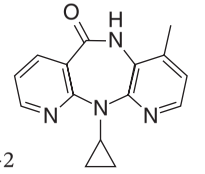
$C_{14}H_9ClF_3NO_2$



154598-52-4

Nevirapine (NVP)

$C_{15}H_{14}N_4O$

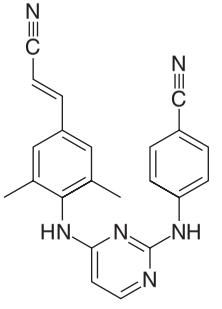


129618-40-2

Rilpivirine (RPV)

$C_{22}H_{18}N_6$

500287-72-9



Doravirin (DOR)

$C_{17}H_{11}ClF_3N_5O_3$

1338225-97-0

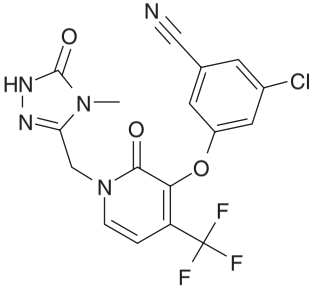


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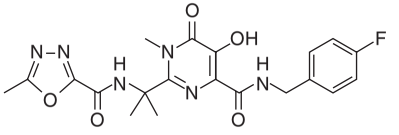
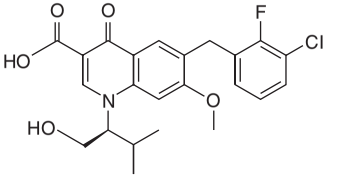
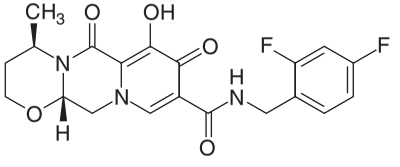
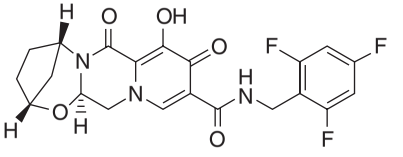
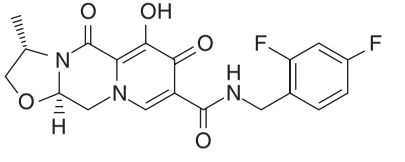
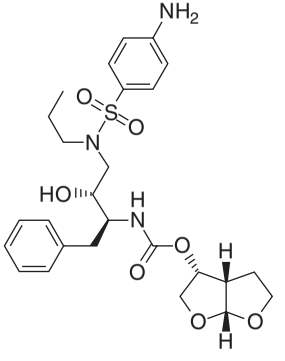
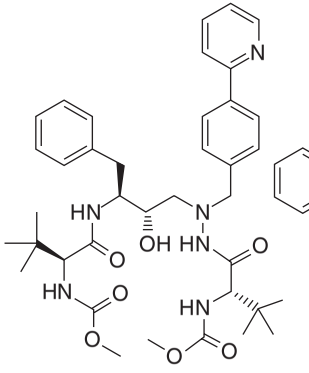
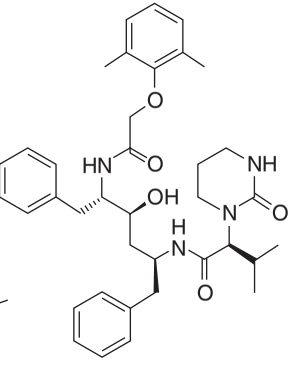
Table 1.2 (Continued)

Drug class: inhibitor of...	Generic drug name/chemical formula/CAS registry no./graphic structure formula	Generic drug name/chemical formula/CAS registry no./graphic structure formula
Integrase strand transfer (INSTI)	Raltegravir (RGV) $C_{20}H_{21}FN_6O_5$ 518048-05-0 	Elvitegravir (EVG) $C_{23}H_{23}ClFNO_5$ 697761-98-1 
	Dolutegravir (DGT) $C_{20}H_{19}F_2N_3O_5$ 1051375-16-6 	Bictegravir (BTG) $C_{21}H_{18}F_3N_3O_5$ 1611493-60-7 
	Cabotegravir[a] $C_{19}H_{17}F_2N_3O_5$ 1051375-10-0	

Protease (PI)	Darunavir (DRV) $C_{27}H_{37}N_3O_7S$ 206361-99-1 	Atazanavir (ATV) $C_{38}H_{52}N_6O_7$ 198904-31-3 	Lopinavir (LPV) $C_{37}H_{48}N_4O_5$ 192725-17-0 
Maturation/capsid	GS-6207[a] GSK3640254[a]	Chemical formula not yet published, CAS registry-no. not yet allocated (as of search on 30 December 2019)	

Source: WIKIPEDIA, the free encyclopedia, as accessed online on 30 December 2019, please also see https://en.wikipedia.org.

a) In clinical study development—refer to public study registry online-resource, available at: https://www.clinicaltrials.gov.

1.3 Currently Open Issues in HIV/AIDS Research

Important milestones in cART development have been achieved in the recent decades as standard of care: complete virus suppression, side-effect- and drug-interaction control, and convenience in taking antiretroviral regimens. Recently observed trends in HIV-treatment include the development of long-acting cART drugs, which are administered alternatively, e.g. injected every eight weeks, or once even less frequently implanted periodically.

When in July 2015 the first results from the START-study (Strategic Timing of Antiretroviral Treatment) were published, the benefit from modern cART for patients with early HIV-infection was evident for the first time [8]. Subsequently, antiretroviral therapy guidelines have changed worldwide and recommend cART for everybody with an HIV-infection, independent from the individual clinical category and CD4-cell count. Thereafter, the global focus of interest was to establish programs that could allow every infected person access to cART. Therefore, the United Nations Program on HIV/AIDS (UNAIDS) have established the 90–90–90-targets, in order to end AIDS as a disease and to control HIV transmissions on a society level [9]. Data on beneficial effects of programs, which lowered the barriers to cART, i.e. linked to HIV transmission control, were published before [10]. Moreover, the exciting confirmation of the SWISS STATEMENT hypothesis (Undetectable HIV leads to zero transmissions) [11] was a major step forward to realize antiretroviral treatment as most effective prevention [12] in the absence of a protective vaccine.

Another major open issue is cure from HIV/AIDS. Albeit individual cases of cure from HIV have been reported [13, 14], e.g. by stem cell transplantation from donors with the rare, intrinsic HIV-resistance due to homozygous CCR5-Δ32/Δ32-gene mutations, stem cell transplantation will hardly be feasible for many patients, as this is associated with substantial risks. Alternative therapeutic procedures using the CRISPR-CASP-technique have been tried, but still require further developments [15]. Beyond stem cell manipulation and/or transplantation, the efforts to induce broadly neutralizing antibodies (BNAPs) remain a second scientific approach to achieve at least "functional cure" from HIV [16].

References

1 CDC (1981). Pneumocystis pneumonia—Los Angeles. *MMWR* 30: 250–252.
2 Barré-Sinoussi, F., Chermann, J.C., Rey, F. et al. (1983). Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 220 (4599): 868–871.
3 Rübsamen-Waigmann, H., Becker, W.B., Helm, E.B. et al. (1986). Isolation of variants of lymphocytopathic retroviruses from the peripheral blood and cerebrospinal fluid of patients with ARC or AIDS. *J. Med. Virol.* 19: 335–344.
4 von Briesen, H., Becker, W.B., Henco, K. et al. (1987). Isolation frequency and growth properties of HIV-variants: multiple simultaneous variants in a patient demonstrated by molecular cloning. *J. Med. Virol.* 23: 51–66.

5 Schwartz, S., Fenyo, E.-M., Felber, B.K., and George, N. (1989). Pavlakis rapidly and slowly replicating human immunodeficiency virus type-1 isolates can be distinguished according to target-cell tropism in T-cell and monocyte cell-lines. *Proceedings of the National Academy of Sciences*, October 1989. doi:https://doi.org/10.1073/pnas.86.18.7200. *Source*: PubMed.

6 Asjö, B., Albert, J., Karlson, A. et al. (1986). *Lancet* ii: 660–662. Tersmette, M., Lange, I.M.A., de Goede, R.E.Y. et al. (1989). *Lancet* i: 983–985.

7 O'Brien, T.R., Rosenberg, P.S., Yellin, F., and Goedert, J.J. (1998). Longitudinal HIV-1 RNA levels in a cohort of homosexual men. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 18 (2): 155–161.

8 INSIGHT START Study Group, Lundgren, J.D., Babiker, A.G. et al. (2015). Initiation of antiretroviral terapy in early asymptomatic HIV infection. *N. Engl. J. Med.* 373 (9): 795–807.

9 WHO (2017). *UNAIDS documents: ending AIDS: progress towards the 90–90–90 targets*, published 20 July 2017. https://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf.

10 Nosyk, B., Min, J., Lima, V.D. et al. (2013). HIV-1 disease progression during highly active antiretroviral therapy: an application using population-level data in British Columbia: 1996–2011. *J. Acquir. Immune Defic. Syndr.* 63 (5): 653–659.

11 Vernazza, P., Hirschel, B., Bernasconi, E., and Flepp, M. (2008). HIV-infizierte Menschen ohne andere STD sind unter wirksamer antiretroviraler Therapie sexuell nicht infektiös. *Bull. Med. Suisses* 89: 165–169.

12 Cohen, M.S., Chen, Y.Q., McCauley, M. et al. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. *N. Engl. J. Med.* 365 (6): 493–505.

13 Hütter, G., Nowak, D., Mossner, M. et al. (2009). Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N. Engl. J. Med.* 360 (7): 692–698.

14 Gupta, R.K., Abdul-Jawad, S., McCoy, L.E. et al. (2019 Apr). HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. *Nature* 568 (7751): 244–248.

15 Xu, L., Wang, J., Liu, Y. et al. (2019). CRISPR-edited stem cells in a patient with HIV and acute lymphocytic leukemia. *N. Engl. J. Med.* 381 (13): 1240–1247.

16 Klein, F., Mouquet, H., Dosenovic, P. et al. (2013). Antibodies in HIV-1 vaccine development and therapy. *Science* 341 (6151): 1199–1204.