HIV infection: epidemiology, pathogenesis, treatment, and prevention

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HIV prevalence is increasing worldwide because people on antiretroviral therapy are living longer, although new infections decreased from 3·3 million in 2002, to 2·3 million in 2012. Global AIDS-related deaths peaked at 2·3 million in 2005, and decreased to 1·6 million by 2012. An estimated 9·7 million people in low-income and middle-income countries had started antiretroviral therapy by 2012. New insights into the mechanisms of latent infection and the importance of reservoirs of infection might eventually lead to a cure. The role of immune activation in the pathogenesis of non-AIDS clinical events (major causes of morbidity and mortality in people on antiretroviral therapy) is receiving increased recognition. Breakthroughs in the prevention of HIV important to public health include male medical circumcision, antiretrovirals to prevent mother-to-child transmission, antiretroviral therapy in people with HIV to prevent transmission, and antiretrovirals for pre-exposure prophylaxis. Research into other prevention interventions, notably vaccines and vaginal microbicides, is in progress.

Epidemiology

The HIV epidemic arose after zoonotic infections with simian immunodeficiency viruses from African primates; bushmeat hunters were probably the first group to be infected with HIV.[1] HIV-1 was transmitted from apes and HIV-2 from sooty mangabey monkeys.[1] Four groups of HIV-1 exist and represent three separate transmission events from chimpanzees (M, N, and O), and one from gorillas (P). Groups N, O, and P are restricted to west Africa. Group M, which is the cause of the global HIV pandemic, started about 100 years ago and consists of nine subtypes: A–D, F–H, J, and K. Subtype C predominates in Africa and India, and accounted for 48% of cases of HIV-1 in 2007 worldwide.[2] Subtype B predominates in western Europe, the Americas, and Australia. Circulating recombinant subtypes are becoming more common.[2] The marked genetic diversity of HIV-1 is a consequence of the error-prone function of reverse transcriptase, which results in a high mutation rate. HIV-2 is largely confined to west Africa and causes a similar illness to HIV-1, but immunodeficiency progresses more slowly and HIV-2 is less transmissible.[1]

In 2012 an estimated 35·3 million people were living with HIV.[3] Sub-Saharan Africa, especially southern Africa, has the highest global burden of HIV (70·8%; figure 1). The global epidemiology of HIV infection has changed markedly as a result of the expanding access to antiretroviral therapy; by 2012, 9·7 million people in low-income and middle-income countries had started antiretroviral therapy.[4] The global prevalence of HIV has increased from 31·0 million in 2002, to 35·3 million in 2012, because people on antiretroviral therapy are living longer,[5] whereas global incidence has decreased from 3·3 million in 2002, to 2·3 million in 2012.[3] The reduction in global HIV incidence is largely due to reductions in heterosexual transmission. Punitive attitudes towards people who inject drugs (especially in eastern Europe) restrict the implementation of opioid substitution treatment and needle and syringe programmes, which are effective prevention strategies that reduce HIV transmission.[6] In regions where the main route of transmission is men who have sex with men (eg, western and central Europe and the Americas), incidence is stable despite high antiretroviral therapy coverage (eg, 75% in Latin America in 2012,[3] and 80% in the UK in 2010).[7] The drivers of the HIV epidemic in men who have sex with men are complex, and include increasing risk behaviour since the introduction of effective antiretroviral therapy (a phenomenon termed therapeutic optimism[8]), high transmission risk of receptive anal intercourse, sexual networks, and stigma restricting access to care.[9]

The number of new infections in children in the 21 priority African countries in the UN Programme on HIV/AIDS (UNAIDS) global plan[10] decreased by 38% between 2009 and 2012, because of increased access to antiretrovirals to prevent mother-to-child transmission. However, access to antiretroviral therapy is much lower in children than adults.[3]

HIV is a major contributor to the global burden of disease. In 2010, HIV was the leading cause of disability-adjusted life years worldwide for people aged 30–44 years, and the fifth leading cause for all ages.[11] Global AIDS-related deaths peaked at 2·3 million in 2005, and decreased to 1·6 million by 2012.[3] About 50% of all deaths

Search strategy and selection criteria

We searched PubMed for publications in English from Jan 1, 2008, to Oct 31, 2013, but did not exclude commonly referenced and highly regarded older publications. We used the search terms "HIV" or "AIDS" in combinations with "epidemiology", "prevention", "pathogenesis", "antiretroviral therapy", "resistance", and "latency". We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are cited to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers.

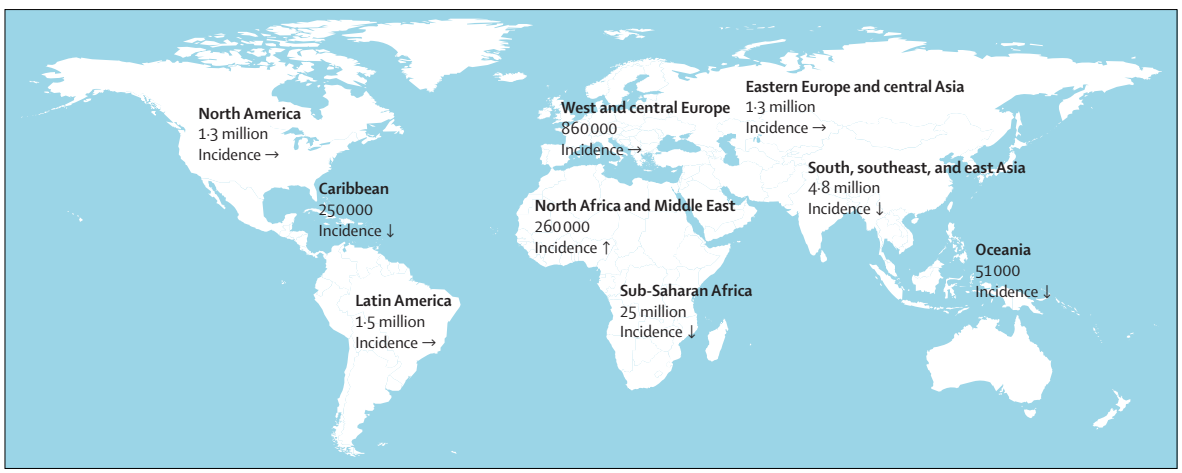

Figure 1: **Estimated number of people living with HIV in 2012 and trends in the incidence of new infections from 2001 to 2012 by global region**
Data from UNAIDS 2013 report.[3]

in people on antiretroviral therapy in high-income countries are not due to AIDS.[12] In one study, major causes of non-AIDS-related deaths were non-AIDS-defining cancers (23·5%), cardiovascular disease (15·7%), and liver disease (14·1%).[12] People with HIV have a 50% increased risk of myocardial infarctions than do people without HIV after adjustment for vascular risk factors.[13] Liver disease is common, mainly because of co-infection with hepatitis B and C, which share similar routes of transmission with HIV.[14]

Tuberculosis continues to be a major cause of morbidity and mortality in low-income and middle-income countries, especially in Africa.[15] Findings of a study[16] done in South Africa in the pre-antiretroviral therapy era showed that tuberculosis doubled within a year after HIV infection, thereafter incidence increased as immunity decreased, and reached a very high incidence of 25·7 per 100 person-years in patients with CD4 T-cell counts lower than 50 cells per μL.[17] Worldwide, HIV-related tuberculosis mortality is decreasing,[15] but many people with HIV in Africa die of undiagnosed tuberculosis.[18]

HIV-1 transmission

The most important factor that increases the risk of sexual transmission of HIV-1 is the number of copies per mL of plasma HIV-1 RNA (viral load), with a 2·4 times increased risk of sexual transmission for every 1 $\log_{10}$ increase.[19] Acute HIV infection, which causes very high plasma viral loads in the first few months, is an important driver of HIV epidemics.[20] A reduction in plasma viral load of 0·7 $\log_{10}$ is estimated to reduce HIV-1 transmission by 50%.[21] Seminal and endocervical viral load independently predict risk of HIV-1 sexual transmission, after adjustment for plasma viral load.[22] Other factors associated with increased risk of sexual transmission of HIV include sexually transmitted infections (notably genital ulcers of any cause,[23] herpes simplex type-2 infection,[24] and bacterial vaginosis[25]), pregnancy,[26] and receptive anal intercourse.[27] Male circumcision is associated with a reduced risk of sexual transmission of HIV.[28]

Findings of some observational studies showed an increased risk of HIV-1 acquisition in women who used long-acting injectable progestogens for contraception, but not with combined oral contraceptives.[29] A health priority in eastern and southern Africa, where the incidence of HIV-1 in young women is very high,[30] is to find out whether long-acting injectable progestogens (the commonest form of contraception used in this region) increase HIV-1 transmission.

Behavioural factors that increase HIV-1 sexual transmission include many sexual partners,[31] and concurrent partnerships.[32] Findings of a study[33] of African heterosexual serodiscordant couples showed that self-reported condom use reduced the per-coital act risk of HIV-1 transmission by 78%.[33] Sex inequality is an important driver of the HIV epidemic, especially in sub-Saharan Africa where women account for 57% of people living with HIV.[3] Injection and non-injection drug use, including alcohol, are associated with increased sexual risk behaviour, whereas injection drug use causes HIV transmission by shared needles.[34] Women who reported intimate partner violence had an increased incidence of HIV infection in a South African study.[35] UNAIDS have identified stigma against HIV, and discrimination and punitive laws against high-risk groups (eg, men who have sex with men, people who inject drugs, and commercial sex workers) as barriers for people to undergo HIV testing, access care, and access prevention measures.[3]

Pathogenesis

HIV life cycle and host immune responses

Figure 2 shows the virus life cycle. The main target of HIV is activated CD4 T lymphocytes; entry is via interactions with CD4 and the chemokine coreceptors, CCR5 or CXCR4. Other cells bearing CD4 and chemokine

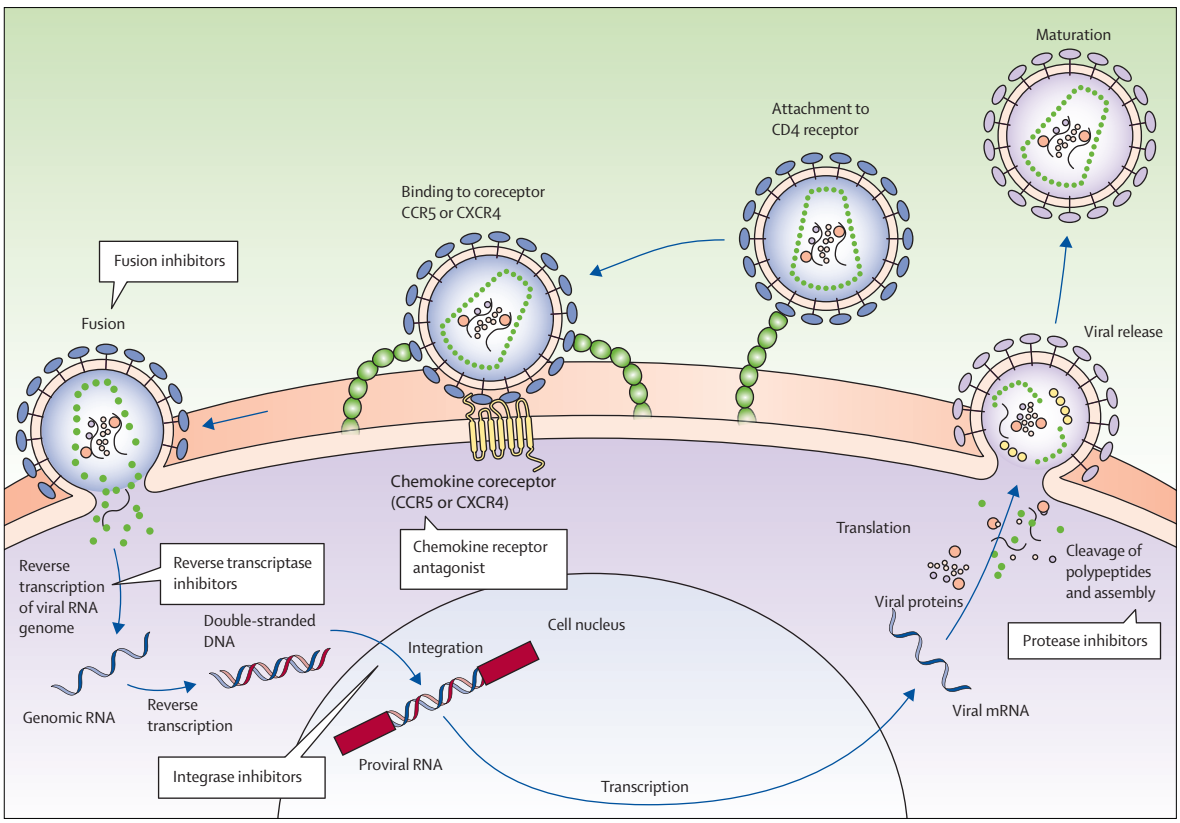

Figure 2: **HIV life cycle showing the sites of action of different classes of antiretroviral drugs**
Adapted from Walker and colleagues,[36] by permission of Elsevier.

receptors are also infected, including resting CD4 T cells, monocytes and macrophages, and dendritic cells. CD4-independent HIV infection of cells can happen, notably in astrocytes[37] and renal epithelial cells,[38] and subsequent HIV gene expression has an important role in the pathogenesis of HIV-associated neurocognitive disorder (related to astrocytes) and nephropathy (related to epithelial cells). A range of host proteins interact with HIV proteins or HIV DNA to either restrict or promote virus replication in specific cell types (table 1).

Transmission of HIV across mucosal membranes is usually established by one founder virus, which has unique phenotypic properties including usage of CCR5 rather than CXR4 for entry,[46] enhanced interaction with dendritic cells, and resistance to interferon-α.[47] Transmission of the founder virus is followed by a rapid increase in HIV replication and then a striking induction of inflammatory cytokines and chemokines, which is in stark contrast to the minimum initial response to other chronic viral infections such as hepatitis B or hepatitis C.[48]

Viral load then decreases to a so-called setpoint, the level of which is established largely by innate and adaptive immune responses (figure 3). HIV-specific CD8 killing of productively infected cells mediated by T cells happens soon after infection, and the potent adaptive immune response to HIV selects for the emergence of mutations in key epitopes, often leading to immune escape.[49] In some HLA types, such as individuals with *HLA-B27* allele infected with clade B, an effective immune response can arise, characterised by HIV-specific T cells with high avidity, polyfunctionality, and capacity to proliferate[50] against both the immunodominant and escaped peptides.[51] However, in nearly all individuals, progressive exhaustion of HIV-specific T cells happens, characterised by high expression of programmed death 1 (PD-1) on both total and HIV-specific T cells and a loss of effector function.[52]

Neutralising antibodies arise roughly 3 months after transmission and select for viral escape mutants.[53] Broadly neutralising antibodies, which can neutralise many HIV-1 subtypes, are produced by about 20% of patients.[54] These antibodies are characterised by a high frequency of somatic mutations that often take years to develop.[55] Broadly neutralising antibodies do not usually provide benefit to the patient because of the development of viral escape mutants.[56] The production of broadly neutralising antibodies by use of new immunogen design strategies is a major focus of vaccine research.[57]

The innate immune response to HIV is largely mediated by natural killer cells, and is also crucial for virus control. Viral escape mutants also emerge, and restrict the antiviral effects of natural killer cells.[58]

Immune dysfunction

The hallmark of HIV infection is the progressive depletion of CD4 T cells because of reduced production and increased destruction. CD4 T cells are eliminated by direct infection,[59] and bystander effects of syncitia formation, immune activation, proliferation, and senescence. In early infection, a transient reduction in circulating CD4 T cells is followed by recovery to near normal concentrations, which then slowly decrease by about 50–100 cells per μL (figure 3).

The most important effect on T-cell homoeostasis happens very early in the gastrointestinal tract, which has a massive depletion of activated CD4 T cells with minimum recovery after antiretroviral therapy.[60] In addition to loss of total CD4 T cells, profound changes in T-cell subsets happen, including preferential loss of T-helper-17 cells,[61] and mucosal-associated invariant T cells, which are crucial for defence against bacteria.[62] The profound depletion of lymphoid cells in the gastrointestinal tract, together with enterocyte apoptosis, and enhanced gastrointestinal tract permeability, leads to increased plasma concentration of microbial products such as lipopolysaccharides.[63] Finally, destruction of the fibroblastic reticular cell network, collagen deposition, and restricted access to the T-cell survival factor interleukin 7 in the lymphoid tissue further contribute to depletion of both CD4-naive and CD8-naive T cells.[64]

Immune activation

HIV infection is also characterised by a marked increase in immune activation, which includes both the adaptive and innate immune systems, and abnormalities in coagulation.[65] The drivers for immune activation include the direct effects of HIV as a ligand for the Toll-like receptor (TLR7 and TLR 8) expressed on plasmacytoid dendritic cells, leading to production of interferon-α;[66] microbial translocation, with lipopolysaccharide as a potent activator or TLR4 leading to the production of pro-inflammatory cytokines such as interleukin 6 and tumour necrosis factor α (TNFα);[63] co-infection with viruses such as cytomegalovirus that induce profound expansion of activated cytomegalovirus-specific T cells;[67] and a reduced ratio of T-helper-17 and regulatory T cells, especially in the gastrointestinal tract.[61]

Evidence of residual inflammation or increased immune activation exists, even in patients with HIV with adequate CD4 T-cell restoration on antiretroviral therapy (figure 3). Markers of residual inflammation in patients with HIV on antiretroviral therapy have been significantly associated with mortality,[68] cardiovascular disease,[69] cancer,[70] neurological disease,[71] and liver disease.[72] Intensification of antiretroviral therapy in participants with virological suppression with the addition of the integrase inhibitor raltegravir reduced T-cell activation in about a third of participants.[73] These data suggest that low-level HIV replication might contribute to persistent inflammation. Treatment of co-infections, such as cytomegalovirus and hepatitis C, reduces T-cell activation too.[74,75]

	Action	HIV target
APOBEC-3G[39]	RNA editing protein	vif
TRIM-5α[40]	E3 ubiquitin ligase tripartite motif targets viral capsid	Capsid
Tetherin (BST-2)[41]	Immunomodulatory membrane protein that inhibits virus budding	vpu
SAMHD1[42,43]	Hydrolyses dNTPs and restricts efficient reverse transcription of HIV	vpx*
TREX-1[44]	Cytosolic exonuclease that inhibits the immune recognition of viral products such as HIV DNA	HIV DNA
LEDGF/p75[45]	Brings HIV DNA in close proximity to chromatin	integrase

APOBEC-3G=apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like-3G. TRIM=tripartide motif. SAM=sterile α motif. HD1=histidine aspartic acid domain-containing protein 1. LEDGF=lens epithelium-derived growth factor. *Expressed by HIV-2 only.

Table 1: **Host proteins that interact with HIV proteins or DNA and either restrict or help with HIV infection in human cells**

Although many studies have identified associations between different biomarkers of inflammation and adverse clinical events, causation in studies in people has been difficult to establish. So far, strategies aimed to reduce residual inflammation in patients with HIV have consisted of small observational studies with surrogate endpoints.[76] Several drugs that are available for other indications (eg, statins, aspirin, angiotensin-converting enzyme inhibitors, and hydroxychloroquine) have the potential to reduce HIV-associated inflammation.[76] Randomised controlled studies are needed to establish whether targeting of inflammation in people with virological suppression on antiretroviral therapy will have a significant clinical effect.

Antiretroviral therapy

Combination antiretroviral therapy regimens that were able to suppress viral replication were developed in the late 1990s and transformed HIV from a progressive illness with a fatal outcome into a chronic manageable disease. More than 25 licensed drugs that block HIV replication at many steps in the virus lifecycle are available (figure 2). Recommended antiretroviral therapy regimens are less toxic, more effective, have a lower pill burden, and are dosed less frequently than the initial protease inhibitor-based regimens. Standard antiretroviral therapy regimens combine two nucleoside reverse transcriptase inhibitors (emtricitabine or lamivudine together with one of abacavir, tenofovir, or zidovudine) with a non-nucleoside reverse transcriptase inhibitor, protease inhibitor, or integrase inhibitor. Several effective nucleoside reverse transcriptase inhibitor-sparing regimens can be used if intolerance or resistance to nucleoside reverse transcriptase inhibitors develops.

After initiation of antiretroviral therapy, the plasma viral load decreases to concentrations below the lower limit of detection of available commercial assays in most people, usually within 3 months (figure 3). By contrast, the recovery of CD4 T cells in individuals on antiretroviral

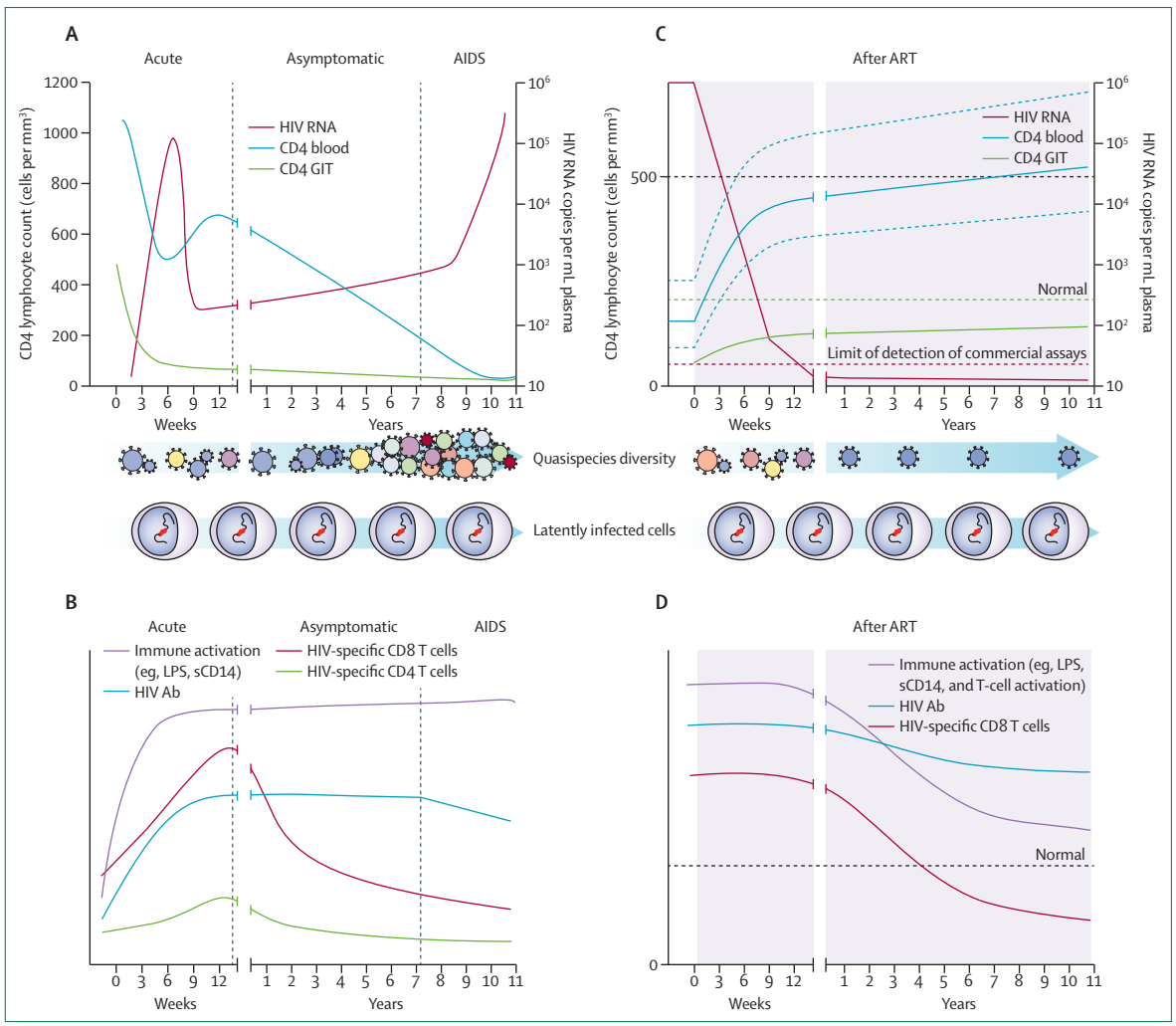

Figure 3: **Natural history of untreated HIV infection and changes after antiretroviral therapy**
(A) In untreated HIV infection, CD4 T cells are progressively lost in blood but CD4 T cells in the gastrointestinal tract are rapidly depleted early on. (B) The acute response to HIV infection includes a dramatic increase in markers of immune activation and production of non-neutralising antibodies and HIV-specific CD4 and CD8 T cells that are associated temporally with a decrease in HIV RNA in blood. (C) After antiretroviral therapy, HIV RNA significantly decreases followed by recovery of CD4 T cells, which varies between individuals (panel). By contrast, recovery of CD4 T cells in the gastrointestinal tract is reduced. (D) With reduction of HIV RNA and viral antigen, HIV-specific T cells decrease after antiretroviral therapy, whereas antibody persists in all patients. Immune activation decreases after antiretroviral therapy but in most patients remains significantly increased compared with healthy controls. GIT=gastrointestinal tract. LPS=lipopolysaccharide.

therapy is variable. In one study[77] of responses to antiretroviral therapy at 6 months in low-income countries, 56% of patients had a successful virological and CD4 response, 19% a virological response without a CD4 response, and 15% a CD4 response without a virological response. Individuals with impaired CD4 T-cell recovery despite virological suppression, which is associated with several risk factors (panel),[78] are at increased risk of adverse outcomes, including serious non-AIDS events.[79] Adjunctive interleukin 2 significantly increases CD4 T-cell counts, but does not result in clinical benefit.[80] Interleukin 7, which enhances proliferation of both naive and memory T cells, also increases CD4 T-cell counts, although whether this results in enhanced clinical benefit is unknown.[81] However, interleukin 7 might have the undesirable effect of expanding the pool of T cells that are latently infected with HIV.[82]

Guidelines in high-income countries allow clinicians to choose a starting regimen of dual nucleoside reverse transcriptase inhibitors combined with either a non-nucleoside reverse transcriptase inhibitor, a ritonavir-boosted protease inhibitor, or an integrase inhibitor, because these three regimens have similar efficacy and tolerability.[83] Subsequent antiretroviral therapy regimen switches for virological failure are guided by the results of resistance testing. For low-income and middle-income countries, WHO recommends a public health approach to use of antiretroviral therapy with standardised first-line (non-nucleoside reverse transcriptase inhibitor plus dual nucleoside reverse transcriptase inhibitors) and second-

line (ritonavir-boosted protease inhibitor plus dual nucleoside reverse transcriptase inhibitors) regimens, and restricted monitoring for both efficacy and toxic effects.[84] Resistance testing is seldom available. Clinical and CD4 count monitoring is used in many low-income countries where viral load monitoring is unavailable, but this monitoring strategy[85] results in both unnecessary switches to second-line therapy and continuation of failing first-line antiretroviral therapy regimens, which will increase the number of resistance mutations. Viral load monitoring would be cost effective in resource-limited settings if low-cost tests, which are available, were used.[86]

Investigators of a study[87] that compared a public health approach with individualised approaches to antiretroviral therapy in people starting treatment in South Africa and Switzerland, reported similar virological outcomes, but the switching rate for toxic effects in Switzerland was higher than in South Africa. Early mortality rates after initiation of antiretroviral therapy are much higher in resource-limited settings than in high-income countries after adjustment for baseline CD4 count, but the difference attenuates after 6 months.[88] Near-normal life expectancy is estimated for patients (other than people who inject drugs) who achieve a normal CD4 count and a suppressed viral load on antiretroviral therapy.[89]

Increasing data suggest that short-course antiretroviral therapy started in early HIV infection might slow disease progression, but further studies of patients presenting with acute infection need to be done.[90] Most international guidelines, including those for low-income and middle-income countries,[84] have increased the CD4 criterion for initiation of antiretroviral therapy to 500 cells per µL or higher, despite no good evidence that antiretroviral therapy initiation at CD4 counts higher than 350 cells per µL provides individual benefit.[91] Increased access to antiretroviral therapy is expected to reduce HIV transmission, but the durability of this effect is unknown, and starting antiretroviral therapy early exposes patients to toxic effects of drugs and the development of resistance before they derive clinical benefit.[92] Retention of patients in care in low-income and middle income countries will be a major challenge because the number of people eligible for antiretroviral therapy will increase from 16·7 million to 25·9 million in 2013, if the WHO 2013 guidelines are introduced.[4] In sub-Saharan Africa, 57% of people are expected to complete eligibility assessment for antiretroviral therapy, and only 65% of people who start treatment remain in care after 3 years.[93] Loss to follow-up increased with increasing population size in a large antiretroviral therapy programme in South Africa.[94] Low rates of retention care are not restricted to low-income and middle-income countries, as shown by a US report[95] that noted that only 51% of patients who were diagnosed with HIV were retained in care in 2010.

Antiretroviral therapy taken in the presence of continuing viral replication will result in the selection of sub-populations of HIV with mutations conferring resistance to antiretroviral drugs. Sub-optimum adherence is the major factor associated with the development of resistance.[96] Antiretroviral drugs differ in their ability to select for resistant mutations. Some drugs (eg, emtricitabine, lamivudine, efavirenz, nevirapine, and raltegravir) rapidly select for one mutation conferring high-level resistance, whereas most other antiretrovirals select for resistance mutations slowly and need several resistant mutations before loss of drug efficacy. Patients who develop antiretroviral resistance can transmit resistant virus to others. The prevalence of antiretroviral resistance in antiretroviral therapy-naive people in high-income countries has reached a plateau of 10–17% with resistance to one or more antiretroviral drugs, whereas the prevalence is steadily increasing in low-income and middle-income countries, reaching 6·6% in 2009.[97] Guidelines for high-income countries recommend a resistance test before initiation of antiretroviral therapy, but this strategy is too expensive to implement in resource-limited settings.

***Panel:* Factors associated with poor CD4 T-cell recovery after antiretroviral therapy**

Host factors
- Older age, low CD4 nadir, high baseline HIV RNA
- HLA type
- Genetic polymorphisms in:
  - Chemokine/chemokine receptors—eg, CCR5D32,
  - Cytokine/cytokine receptors—eg, interleukin 7 receptor
  - Fas/Fas ligand

Viral factors
- CXCR4 using virus
- Co-infection with cytomegalovirus, hepatitis C virus, or GB virus C

Immunological factors
- Low thymic output
- Poor bone marrow function
- Increased immune activation
- Proliferation
- Senescence
- Increased PD-1 expression
- Increased apoptosis

Immune reconstitution disease

Immune reconstitution disease, also called immune reconstitution inflammatory syndrome, is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which happens shortly after initiation of antiretroviral therapy.[98] Most commonly, the antigens triggering immune reconstitution disease are from opportunistic infections, notably tuberculosis, cryptococcal meningitis, and cytomegalovirus retinitis.[99] Immune reconstitution disease is common, with an overall

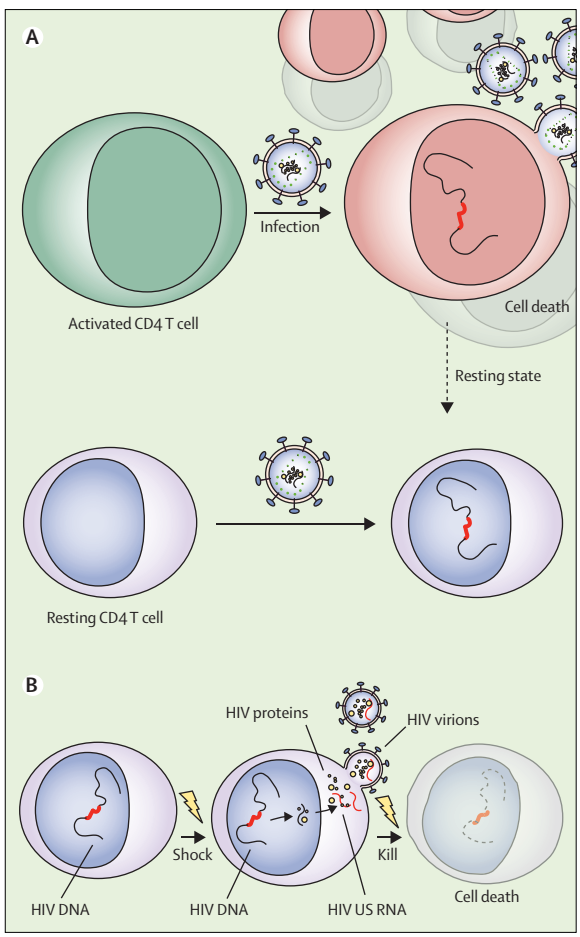

Figure 4: **Latency and activation of cellular HIV infection**
(A) Latency can be established via survival of an activated infected T cell, which reverts to a memory state, or after direct infection of a resting CD4 T cell in the presence of appropriate signalling mediated by either chemokines or cell-to-cell signalling. (B) Activating transcription from latency will induce HIV transcription (with an increase in cell associated unspliced RNA), HIV protein, and virion production with the aim of cell death induction by either virus-induced cytolysis or stimulation of HIV-specific cytotoxic T cells. Additional interventions that kill the cell might also be needed

incidence of 16·1% reported in a systematic review.[99] The disease causes high morbidity, but mortality is low (4·5%), except with cryptococcal meningitis immune reconstitution disease (20·8% mortality). Findings of a small randomised controlled trial[100] showed benefit of adjunctive prednisone in participants with tuberculosis-associated immune reconstitution disease. Immune reconstitution disease happens more commonly when antiretroviral therapy is started in patients with low CD4 counts or soon after starting treatment for the opportunistic infection. Strategies to reduce immune reconstitution disease include initiation of antiretroviral therapy at high CD4 counts, delayed initiation of antiretroviral therapy in patients with an infection (especially if infection includes the CNS), and screening for and prevention of opportunistic infections before initiation of antiretroviral therapy.[98]

Latency, reservoirs, and potential cure

Despite great successes of antiretroviral therapy in the control of HIV replication and significant reduction of morbidity and mortality, antiretroviral therapy is unable to cure HIV and life-long treatment is needed. HIV can persist in patients on antiretroviral therapy because of resting memory T cells that are long-lived and latently infected,[101] residual replication in some individuals,[73] and anatomical reservoirs such as the gastrointestinal tract,[102] lymphoid tissue, and the CNS.[103]

Latency is defined as integration of HIV DNA into the host genome in the absence of virus production. Latency can be established in vitro via direct infection of resting CD4 T cells in the presence of specific chemokines,[104] or after reversion of an activated infected T cell to a resting state (figure 4).[105] Latency has been shown in vivo in central and transitional memory T cells,[101,106] and in naive T cells.[107] Latency can also be established in monocyte-macrophages[108] and astrocytes,[109] but the importance of these cells to virus persistence in patients on antiretroviral therapy is unclear.

Many factors restrict efficient HIV transcription from the integrated provirus in latently infected resting CD4 T cells including the sub-nuclear localisation of the provirus, the absence of transcription factors such as NF-kB and nuclear factor of activated T cells, the presence of transcriptional repressors, the epigenetic control of the HIV promoter (including histone modification by acetylation and methylation, and DNA modification), and sub-optimum concentrations of the virus protein *tat*.[110] Additionally, post-transcriptional blocks including microRNAs restrict viral translation in resting T cells.[111] Finally, latently infected T cells can undergo homoeostatic proliferation[106] via stimulation from homoeostatic cytokines such as interleukin 7,[82] which further contribute to their long half-life and persistence.

Much interest surrounds the discovery of either a functional cure (long-term control of HIV without antiretroviral therapy) or a sterilising cure (complete elimination of all HIV-infected cells). Hopes that a cure might be possible have been raised by a case report of a man who underwent stem cell transplants for leukaemia,[112] and an infant who started antiretroviral therapy soon after delivery.[113] The best documented report of cure is the Berlin patient,[112] a man with HIV on antiretroviral therapy who had acute myeloid leukaemia and received two bone marrow transplants from a donor with a homozygous defect in CCR5, a key coreceptor needed by HIV for cell entry. Shortly after transplantation, the patient ceased antiretroviral therapy and minimum or no virus has been detected in plasma or tissue for more than 6 years.[114] This case has inspired the development of gene therapy to eliminate CCR5 in patient-derived T cells and stem cells with new technologies such as zinc finger nucleases that can effectively eliminate CCR5 expression.[115]

Early initiation of antiretroviral therapy alone might have a substantial effect on reduction of the reservoir and

preservation of effective immune function. Long-term control of low-level viraemia after cessation of antiretroviral therapy has been reported in 1–15% of individuals who initiated antiretroviral therapy in acute infection.[116,117] Very early initiation of antiretroviral therapy might restrict infection of long-lived central memory T cells that have been latently infected.[118]

Another approach to cure HIV is to eliminate latently infected T cells. One strategy under investigation is the activation of latent HIV, which will induce expression of viral proteins leading to immune-mediated clearance or cytolysis of infected cells (figure 4). In vitro, many compounds can activate HIV production from latency, including histone deacetylase inhibitors, methylation inhibitors, activators of NF-kB such as prostratin, and other compounds including disulfiram.[119] Results of the first studies of the histone deacetylase inhibitor vorinostat, showed an increase in HIV transcription,[120,121] but it remains unclear whether activation alone effectively eliminates latently infected cells, as suggested by one in-vitro model of HIV latency.[122] Additionally, boost of HIV-specific T-cell immunity might be needed, with either therapeutic vaccination or immuno-modulation. Up to now, therapeutic vaccination to allow cessation of antiretroviral therapy has yielded disappointing results,[123] although recent vaccine trials with dendritic cells[124] and a cytomegalovirus vector in a simian model[125] have shown promise.[126]

Prevention

Mother-to-child HIV-1 transmission

During the past two decades, remarkable progress has been made in the risk reduction of perinatal HIV-1 transmission. Knowledge about the timing of HIV-1 transmission to infants has allowed the development of appropriate interventions. The risk of HIV-1 transmission to the infant is about 25% at delivery in the absence of interventions, with most of the risk arising after 36 weeks and especially intrapartum.[127] HIV-1 transmission happens at a rate of 8·9 per 100 child-years of breastfeeding after the fourth week,[128] with higher rates during the first 4 weeks.[119] Mixed feeding roughly doubles the risk of HIV-1 transmission compared with exclusive breastfeeding.[127] Prolonged breastfeeding is the norm in most resource-poor settings, where the risk of transmitting HIV-1 to children reached about 40% without interventions. Recommended mother-to-child HIV-1 transmission interventions have resulted in a ten times reduction in this risk, and complete elimination of mother-to-child HIV-1 transmission is now feasible.

Antiretroviral therapy is the mainstay of prevention of mother-to-child HIV-1 transmission. Antepartum zidovudine monotherapy, augmented with one dose of nevirapine during labour, was an effective and affordable intervention, but it has been superseded by standard combination antiretroviral therapy for women who do not qualify for continuing antiretroviral therapy. Combination antiretroviral therapy is more effective at prevention of mother-to-child HIV-1 transmission than zidovudine plus one dose of nevirapine,[129] and has the additional advantages of reducing sexual HIV transmission and reducing HIV-associated morbidity and mortality. Antiretroviral therapy should ideally be started after the first trimester, provided that women are well enough to wait. In resource-limited settings the reduction in infant HIV transmission by formula feeding is offset by a higher infant mortality,[130] which shows the crucial role that breastfeeding has in child health. Strategies to reduce HIV transmission from breastfeeding in resource-limited settings include the use of antiretroviral monotherapy to infants,[131] or continuing combination antiretroviral therapy until weaning in mothers who do not qualify for ongoing antiretroviral therapy.[129,132] WHO recommends either continuing combination antiretroviral therapy until weaning or for life in pregnant women with HIV who do not qualify for continuing antiretroviral therapy.[84]

Antiretrovirals alone will not reach the goal of elimination of prevention of mother-to-child HIV-1 transmission. Access to antenatal care, HIV testing, and mother-to-child HIV-1 transmission interventions will need to be substantially increased in regions with high HIV prevalence.[133] In Africa, uptake of mother-to-child HIV-1 transmission interventions was improved if the male partner was included, but this is often difficult to achieve.[133] In low-income and middle-income countries, many women present late for antenatal care or deliver without antenatal care; therefore, HIV transmission to infants will be higher than when antiretroviral therapy is started at the optimum time of about 14 weeks. A further challenge to the implementation of antiretroviral therapy for mothers to prevent transmission from breastfeeding is that antiretroviral therapy adherence post partum has been found to be significantly lower than antepartum in a recent meta-analysis.[134] Studies of interventions to improve post-partum adherence to antiretroviral therapy are urgently needed. Last, in view of the annual HIV-1 incidence rates of up to 10% in some areas of southern Africa, a crucial priority for prevention of mother-to-child HIV-1 transmission is to reduce new HIV infections in young women, which would lead to fewer HIV-1 infected pregnant women and infants.

Sexual HIV transmission

Prevention of sexual HIV transmission has been a priority since the beginning of the epidemic. No one prevention intervention is effective enough on its own, and many interventions are necessary to control the epidemic. Several major advances have been made in research on prevention intervention in the past 5 years, especially including the use of antiretrovirals. The most potent intervention to reduce sexual transmission of HIV is antiretroviral therapy, as shown by findings of the landmark HPTN 052 study.[135] In this study the partner with HIV from a serodiscordant couple with CD4 counts

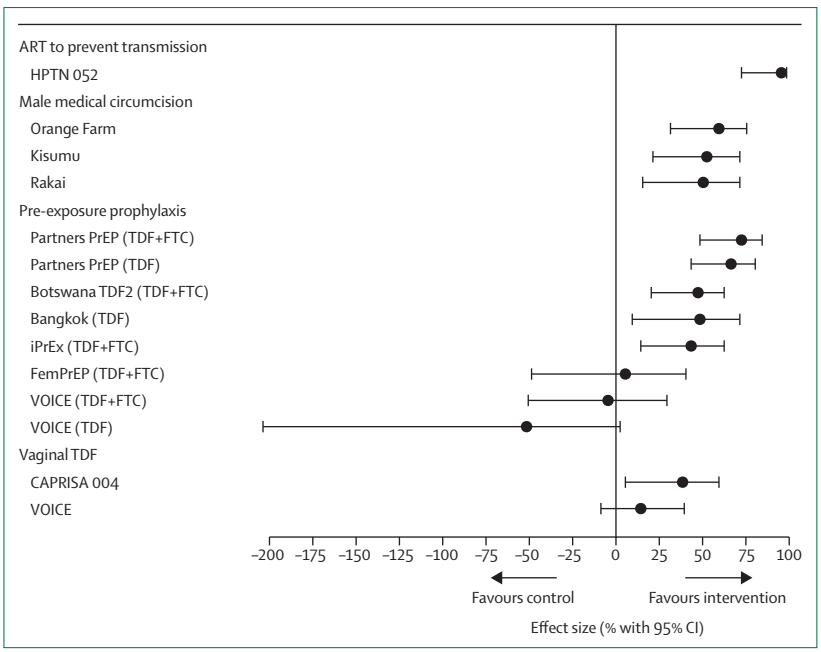

Figure 5: **Clinical trials of interventions to prevent sexual transmission of HIV-1**
TDF=tenofovir. FTC=emtricitabine. References for studies: HPTN052;[135] Orange Farm;[141] Kisumu;[142] Rakai;[143] Partners PrEP;[144] Botswana TDF2;[145] Bangkok;[146] iPrEX;[147] FemPrEP;[148] VOICE;[149] CAPRISA 004.[150]

of 350–550 cells per μL were randomised to receive immediate antiretroviral therapy or deferred antiretroviral therapy (when two CD4 counts were <250 cells per μL). Immediate antiretroviral therapy was associated with a 96% reduction in HIV transmission events, in the context of almost universal viral suppression. Results of HPTN 052 also showed the need for complementary prevention interventions, because 25% of HIV transmissions were not from the infected partner. The public health effect of antiretroviral therapy coverage was assessed in rural KwaZulu-Natal, South Africa, an area with very high HIV prevalence.[136] The risk of HIV acquisition was associated with antiretroviral therapy coverage in the local community. HIV acquisition was 38% lower in communities with high antiretroviral therapy coverage, defined as 30–40% among all HIV-infected people, than in communities with antiretroviral therapy coverage of less than 10%.[136] The population-level effect of earlier antiretroviral therapy initiation at all CD4 counts, the so-called test and treat strategy, is being studied in randomised trials.

The feasibility of achievement of the benefits of antiretroviral therapy will need effective interventions to greatly increase knowledge of HIV status (achieved in Project Accept[137] through community mobilisation and mobile HIV testing), and near universal testing (accomplished through home-based HIV testing).[138] Effective messaging will be needed to motivate people to initiate antiretroviral therapy when they are asymptomatic and at high CD4 counts, and to address barriers to linkages between HIV care and retention in care.[139] A cautionary point about the introduction of the test and treat strategy is that it could increase antiretroviral resistance.[140]

Pre-exposure prophylaxis with daily oral tenofovir or tenofovir plus emtricitabine effectively reduced HIV acquisition in four of six trials (figure 5). The efficacy of pre-exposure prophylaxis ranged from 44% to 75%, and was strongly associated with adherence (table 2). Factors that affect risk perception, uptake of pre-exposure prophylaxis, and adherence to pre-exposure prophylaxis need to be studied in different populations at high risk for HIV.

Vaginal and, more recently, rectal microbicides are attractive interventions because, unlike condoms, they are under the control of the receptive partner. Findings of 12 clinical trials of vaginal microbicides with non-specific activity against HIV and sexually transmitted infections failed to show efficacy.[151] The emphasis has shifted to vaginal microbicides that target different stages of the HIV life cycle.[152] Results of the CAPRISA 004 trial[150] in South Africa showed that pericoital use of 1% tenofovir gel reduced HIV acquisition by 39%. By contrast, in the VOICE trial[149] the daily 1% tenofovir gel group was stopped early because of absence of efficacy. The results of the FACTS 001 study (NCT01386294), a confirmatory trial of pericoital use of 1% tenofovir gel, are awaited. In recognition of the challenges with daily or pericoital dosing of topical microbicides, novel delivery strategies are being assessed with slow drug-eluting delivery devices, such as intra-vaginal rings containing antiretrovirals.[153]

Medical male circumcision is an effective HIV prevention intervention, which significantly decreased HIV acquisition in men (incidence risk ratio 0·5 at 12 months compared with men randomised to the control group who were not circumcised) in a meta-analysis of three randomised controlled trials done in Africa.[154] In high-risk communities in Africa, for every eight operations done, one HIV infection is expected to be averted, and the rate of male-to-female HIV transmission after medical male circumcision is reduced by 46%.[155] Medical male circumcision is cost-saving in sub-Saharan Africa.[156] Task shifting of medical male circumcision from doctors to non-physician clinicians is safe,[157] and would help scale up in low-income countries. Despite the potential public health benefits of medical male circumcision, the past 5 years have shown several scale-up challenges.[158] Many strategies are needed to increase demand for medical male circumcision, including promotion of benefits of circumcision to men and their female partners, and supply-side interventions to provide medical male circumcision through mobile clinics and devices that reduce procedure time.[158] Findings of meta-analyses of studies in several different risk groups and regions have shown that behavioural interventions reduce self-reported risk behaviour.[126,159–162] Findings of some studies of behavioural interventions showed that condom use reduced the incidence of HIV infection.[160,163] Voluntary counselling and testing for HIV reduces the number of

self-reported sexual partners, but the benefit is largely confined to people with HIV.[164]

Other interventions to reduce HIV infectiousness have focused on treatment of co-infections, notably herpes simplex type-2 infection, which causes genital herpes. Aciclovir and valaciclovir decrease plasma and genital HIV concentrations.[165] To establish whether the magnitude of HIV suppression was sufficient to reduce HIV transmission, a placebo-controlled trial was done in African HIV serodiscordant couples, aciclovir reduced plasma HIV concentrations by 0·25 $\log_{10}$, which was not associated with decreased HIV transmission,[166] but delayed HIV disease progression slightly.[167] Increased doses of valaciclovir achieved significantly higher reductions in plasma HIV concentrations.[168] Additional research is needed to define the role of other interventions to treat co-infections.[169] The first trial of population-based interventions to control sexually transmitted infections showed a reduction in HIV incidence,[170] but three subsequent trials and a meta-analysis reported no significant effect on HIV incidence.[171]

Vaccines

Big challenges face the development of an effective HIV vaccine, including the genetic diversity of HIV, uncertainty about what constitutes protective immunity, and difficulty in the development of antigens that are highly immunogenic. Findings of clinical trials of HIV vaccines have eliminated several candidate vaccines that have not shown efficacy. One trial[172] of a prime-boost HIV vaccine strategy that used an adenovirus vector resulted in an increased rate of HIV infections in the active group in uncircumcised men and men who had pre-existing antibodies to the adenovirus vector serotype. The RV144 trial[173] done in Thailand, provided the only evidence up to now that vaccine protection could be achieved with a 31% reduction in HIV acquisition. Immune correlates of protection from the RV144 trial,[174] together with new vector approaches that improve the breadth of T-cell responses and identify targets for broadly neutralising antibodies, will hopefully result in the development of more effective vaccines.[175]

Conclusions

HIV continues to be a major contributor to the global burden of disease, especially in sub-Saharan Africa. Antiretroviral therapy is changing the global epidemiology of HIV by increasing prevalence because of reductions in AIDS deaths, and is contributing to decreasing HIV incidence by reduction of the risk of transmission. HIV incidence in men who have sex with men is not decreasing despite high antiretroviral therapy coverage. The drivers of the HIV epidemic in men who have sex with men include increasing risk behaviour since the introduction of effective antiretroviral therapy, the high transmission risk of receptive anal intercourse, sexual networks, and stigma restricting access to care. In injection drug users stigma plays a major part in restriction of access to interventions that prevent HIV and care for those who are HIV-positive. Immune activation, which is reduced but not abolished by antiretroviral therapy, plays an important part in the pathogenesis of vascular disease, the risk of which is increased in HIV infection. Improved understanding of viral latency and reservoirs might result in a cure. Recent advances in the prevention of HIV have been dominated by the role of antiretroviral drugs in reduction of mother-to-child transmission and as pre-exposure prophylaxis in high risk groups. The use of antiretroviral therapy in early HIV infection to reduce transmission is being studied in randomised controlled trials, but there will be implementation challenges in countries with a generalised HIV epidemic. An effective vaccine remains elusive despite two decades of effort.

	Efficacy of tenofovir-emtricitabine compared with placebo	Adherence*
Partners PrEP[144]	75%	82%
Botswana TDF2[145]	62%	79%
Bangkok Tenofovir Study[146]	49%	67%
iPrEx[147]	44%	51%
Fem-PrEP[148]	6%	26%
VOICE[149]	−4·2%	29%

*Assessed by plasma tenofovir concentrations.

Table 2: **Association between adherence and efficacy of oral tenofovir-emtricitabine for the prevention of HIV-1 acquisition in trials of pre-exposure prophylaxis**

Contributors

All authors contributed equally.

Declaration of interests

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References

1 Sharp PM, Hahn BH. Origins of HIV and the AIDS pandemic. *Cold Spring Harb Perspect Med* 2011; **1:** 006841.

2 Hemelaar J, Gouws E, Ghys PD, Osmanov S, for the WHO-UNAIDS Network for HIV Isolation and Characterisation. Global trends in molecular epidemiology of HIV-1 during 2000–2007. *AIDS* 2011; **25:** 679–89.

3 UNAIDS. Report on the global AIDS epidemic 2013. http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf (accessed Nov 9, 2013).

4 WHO. Global update on HIV treatment 2013: results, impact and opportunities. June 2013. Geneva, Switzerland; World Health Organization, 2013.

5 Zaidi J, Grapsa E, Tanser F, Newell ML, Barnighausen T. Dramatic increases in HIV prevalence after scale-up of antiretroviral treatment: a longitudinal population-based HIV surveillance study in rural kwazulu-natal. *AIDS* 2013; **27:** 2301–05.

6 Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. *Lancet* 2010; **376:** 285–301.

7 Birrell PJ, Gill ON, Delpech VC, et al. HIV incidence in men who have sex with men in England and Wales 2001–10: a nationwide population study. *Lancet Infect Dis* 2013; **13:** 313–18.

8 Mayer KH, Mimiaga MJ. Past as prologue: the refractory and evolving HIV epidemic among men who have sex with men. *Clin Infect Dis* 2011; **52:** 1371–73.

9 Beyrer C, Sullivan P, Sanchez J, et al. The global HIV epidemics in MSM: time to act. *AIDS* 2013; **27:** 2665–78.

10 UNAIDS. 2013 progress report on the global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Nov, 2013. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/20130625_progress_global_plan_en.pdf (accessed Jan 30, 2014).

11 Ortblad KF, Lozano R, Murray CJ. The burden of HIV: insights from the GBD 2010. *AIDS* 2013; **27:** 2003–17.

12 Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis* 2010; **50:** 1387–96.

13 Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med* 2013; **173:** 614–22.

14 Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. *Lancet* 2011; **377:** 1198–209.

15 Glaziou P, Falzon D, Floyd K, Raviglione M. Global epidemiology of tuberculosis. *Semin Respir Crit Care Med* 2013; **34:** 3–16.

16 Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *J Infect Dis* 2005; **191:** 150–58.

17 Holmes CB, Wood R, Badri M, et al. CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. *J Acquir Immune Defic Syndr* 2006; **42:** 464–69.

18 Cohen T, Murray M, Wallengren K, Alvarez GG, Samuel EY, Wilson D. The prevalence and drug sensitivity of tuberculosis among patients dying in hospital in KwaZulu-Natal, South Africa: a postmortem study. *PLoS Med* 2010; **7:** e1000296.

19 Quinn TC, Wawer MJ, Sewankambo N, et al, and the Rakai Project Study Group. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **342:** 921–29.

20 Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 Infection. *N Engl J Med* 2011; **364:** 1943–54.

21 Lingappa JR, Hughes JP, Wang RS, et al, and the Partners in Prevention HSV/HIV Transmission Study Team. Estimating the impact of plasma HIV-1 RNA reductions on heterosexual HIV-1 transmission risk. *PLoS One* 2010; **5:** e12598.

22 Baeten JM, Kahle E, Lingappa JR, et al, and the Partners in Prevention HSV/HIV Transmission Study Team. Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission. *Sci Transl Med* 2011; **3:** 77ra29.

23 Røttingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis* 2001; **28:** 579–97.

24 Glynn JR, Biraro S, Weiss HA. Herpes simplex virus type 2: a key role in HIV incidence. *AIDS* 2009; **23:** 1595–98.

25 Atashili J, Poole C, Ndumbe PM, Adimora AA, Smith JS. Bacterial vaginosis and HIV acquisition: a meta-analysis of published studies. *AIDS* 2008; **22:** 1493–501.

26 Mugo NR, Heffron R, Donnell D, et al, and the Partners in Prevention HSV/HIV Transmission Study Team. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples. *AIDS* 2011; **25:** 1887–95.

27 Baggaley RF, White RG, Boily MC. HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention. *Int J Epidemiol* 2010; **39:** 1048–63.

28 Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *AIDS* 2000; **14:** 2361–70.

29 Polis CB, Curtis KM. Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence. *Lancet Infect Dis* 2013; **13:** 797–808.

30 Butler AR, Smith JA, Polis CB, Gregson S, Stanton D, Hallett TB. Modelling the global competing risks of a potential interaction between injectable hormonal contraception and HIV risk. *AIDS* 2013; **27:** 105–13.

31 Tanser F, Bärnighausen T, Hund L, Garnett GP, McGrath N, Newell ML. Effect of concurrent sexual partnerships on rate of new HIV infections in a high-prevalence, rural South African population: a cohort study. *Lancet* 2011; **378:** 247–55.

32 Epstein H, Morris M. Concurrent partnerships and HIV: an inconvenient truth. *J Int AIDS Soc* 2011; **14:** 13.

33 Hughes JP, Baeten JM, Lingappa JR, et al, and the Partners in Prevention HSV/HIV Transmission Study Team. Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. *J Infect Dis* 2012; **205:** 358–65.

34 Crawford ND, Vlahov D. Progress in HIV reduction and prevention among injection and noninjection drug users. *J Acquir Immune Defic Syndr* 2010; **55** (suppl 2)**:** S84–87.

35 Jewkes RK, Dunkle K, Nduna M, Shai N. Intimate partner violence, relationship power inequity, and incidence of HIV infection in young women in South Africa: a cohort study. *Lancet* 2010; **376:** 41–48.

36 Davidson's Principles and Practice of Medicine, 22nd edn. Walker BR, Colledge NR, Ralston SH, Penman I, eds. London, UK: Churchill Livingstone. 2014.

37 Liu Y, Liu H, Kim BO, et al. CD4-independent infection of astrocytes by human immunodeficiency virus type 1: requirement for the human mannose receptor. *J Virol* 2004; **78:** 4120–33.

38 Chen P, Chen BK, Mosoian A, et al. Virological synapses allow HIV-1 uptake and gene expression in renal tubular epithelial cells. *J Am Soc Nephrol* 2011; **22:** 496–507.

39 Sheehy AM, Gaddis NC, Malim MH. The antiretroviral enzyme APOBEC3G is degraded by the proteasome in response to HIV-1 Vif. *Nat Med* 2003; **9:** 1404–07.

40 Stremlau M, Owens CM, Perron MJ, Kiessling M, Autissier P, Sodroski J. The cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World monkeys. *Nature* 2004; **427:** 848–53.

41 Neil SJ, Zang T, Bieniasz PD. Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu. *Nature* 2008; **451:** 425–30.

42 Hrecka K, Hao C, Gierszewska M, et al. Vpx relieves inhibition of HIV-1 infection of macrophages mediated by the SAMHD1 protein. *Nature* 2011; **474:** 658–61.

43 Laguette N, Sobhian B, Casartelli N, et al. SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx. *Nature* 2011; **474:** 654–57.

44 Yan N, Regalado-Magdos AD, Stiggelbout B, Lee-Kirsch MA, Lieberman J. The cytosolic exonuclease TREX1 inhibits the innate immune response to human immunodeficiency virus type 1. *Nat Immunol* 2010; **11:** 1005–13.

45 Maertens G, Cherepanov P, Pluymers W, et al. LEDGF/p75 is essential for nuclear and chromosomal targeting of HIV-1 integrase in human cells. *J Biol Chem* 2003; **278:** 33528–39.

46 Keele BF, Giorgi EE, Salazar-Gonzalez JF, et al. Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection. *Proc Natl Acad Sci USA* 2008; **105:** 7552–57.

47 Parrish NF, Gao F, Li H, et al. Phenotypic properties of transmitted founder HIV-1. *Proc Natl Acad Sci USA* 2013; **110:** 6626–33.

48 Stacey AR, Norris PJ, Qin L, et al. Induction of a striking systemic cytokine cascade prior to peak viremia in acute human immunodeficiency virus type 1 infection, in contrast to more modest and delayed responses in acute hepatitis B and C virus infections. *J Virol* 2009; **83:** 3719–33.

49 Goonetilleke N, Liu MK, Salazar-Gonzalez JF, et al, and the CHAVI Clinical Core B. The first T cell response to transmitted/founder virus contributes to the control of acute viremia in HIV-1 infection. *J Exp Med* 2009; **206:** 1253–72.

50 Almeida JR, Price DA, Papagno L, et al. Superior control of HIV-1 replication by CD8+ T cells is reflected by their avidity, polyfunctionality, and clonal turnover. *J Exp Med* 2007; **204:** 2473–85.

51 Ladell K, Hashimoto M, Iglesias MC, et al. A molecular basis for the control of preimmune escape variants by HIV-specific CD8+ T cells. *Immunity* 2013; **38:** 425–36.

52 Trautmann L, Janbazian L, Chomont N, et al. Upregulation of PD-1 expression on HIV-specific CD8+ T cells leads to reversible immune dysfunction. *Nat Med* 2006; **12:** 1198–202.

53 Richman DD, Wrin T, Little SJ, Petropoulos CJ. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. *Proc Natl Acad Sci USA* 2003; **100:** 4144–49.

54 Walker LM, Huber M, Doores KJ, et al, and the Protocol G Principal Investigators. Broad neutralization coverage of HIV by multiple highly potent antibodies. *Nature* 2011; **477:** 466–70.

55 Klein F, Diskin R, Scheid JF, et al. Somatic mutations of the immunoglobulin framework are generally required for broad and potent HIV-1 neutralization. *Cell* 2013; **153:** 126–38.

56 Liao HX, Lynch R, Zhou T, et al, and the NISC Comparative Sequencing Program. Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus. *Nature* 2013; **496:** 469–76.

57 Jardine J, Julien JP, Menis S, et al. Rational HIV immunogen design to target specific germline B cell receptors. *Science* 2013; **340:** 711–16.

58 Alter G, Heckerman D, Schneidewind A, et al. HIV-1 adaptation to NK-cell-mediated immune pressure. *Nature* 2011; **476:** 96–100.

59 Cooper A, García M, Petrovas C, Yamamoto T, Koup RA, Nabel GJ. HIV-1 causes CD4 cell death through DNA-dependent protein kinase during viral integration. *Nature* 2013; **498:** 376–79.

60 Mehandru S, Poles MA, Tenner-Racz K, et al. Mechanisms of gastrointestinal CD4+ T-cell depletion during acute and early human immunodeficiency virus type 1 infection. *J Virol* 2007; **81:** 599–612.

61 Prendergast A, Prado JG, Kang YH, et al. HIV-1 infection is characterized by profound depletion of CD161+ Th17 cells and gradual decline in regulatory T cells. *AIDS* 2010; **24:** 491–502.

62 Cosgrove C, Ussher JE, Rauch A, et al. Early and nonreversible decrease of CD161++ /MAIT cells in HIV infection. *Blood* 2013; **121:** 951–61.

63 Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* 2006; **12:** 1365–71.

64 Zeng M, Southern PJ, Reilly CS, et al. Lymphoid tissue damage in HIV-1 infection depletes naïve T cells and limits T cell reconstitution after antiretroviral therapy. *PLoS Pathog* 2012; **8:** e1002437.

65 Lichtfuss GF, Hoy J, Rajasuriar R, Kramski M, Crowe SM, Lewin SR. Biomarkers of immune dysfunction following combination antiretroviral therapy for HIV infection. *Biomarkers Med* 2011; **5:** 171–86.

66 Meier A, Chang JJ, Chan ES, et al. Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. *Nat Med* 2009; **15:** 955–59.

67 Hsue PY, Hunt PW, Sinclair E, et al. Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses. *AIDS* 2006; **20:** 2275–83.

68 Kuller LH, Tracy R, Belloso W, et al, and the INSIGHT SMART Study Group. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med* 2008; **5:** e203.

69 Hsue PY, Scherzer R, Hunt PW, et al. Carotid intima-media thickness progression in HIV-infected adults occurs preferentially at the carotid bifurcation and is predicted by inflammation. *J Am Heart Assoc* 2012; **1.**

70 Marks MA, Rabkin CS, Engels EA, et al. Markers of microbial translocation and risk of AIDS-related lymphoma. *AIDS* 2013; **27:** 469–74.

71 Ancuta P, Kamat A, Kunstman KJ, et al. Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. *PLoS One* 2008; **3:** e2516.

72 Andrade BB, Hullsiek KH, Boulware DR, et al, and the INSIGHT Study Group. Biomarkers of inflammation and coagulation are associated with mortality and hepatitis flares in persons coinfected with HIV and hepatitis viruses. *J Infect Dis* 2013; **207:** 1379–88.

73 Buzón MJ, Massanella M, Llibre JM, et al. HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. *Nat Med* 2010; **16:** 460–65.

74 Hunt PW, Martin JN, Sinclair E, et al. Valganciclovir reduces T cell activation in HIV-infected individuals with incomplete CD4+ T cell recovery on antiretroviral therapy. *J Infect Dis* 2011; **203:** 1474–83.

75 Gonzalez VD, Falconer K, Blom KG, et al. High levels of chronic immune activation in the T-cell compartments of patients coinfected with hepatitis C virus and human immunodeficiency virus type 1 and on highly active antiretroviral therapy are reverted by alpha interferon and ribavirin treatment. *J Virol* 2009; **83:** 11407–11.

76 Rajasuriar R, Khoury G, Kamarulzaman A, French MA, Cameron PU, Lewin SR. Persistent immune activation in chronic HIV infection: do any interventions work? *AIDS* 2013; **27:** 1199–208.

77 Tuboi SH, Brinkhof MW, Egger M, et al. Discordant responses to potent antiretroviral treatment in previously naive HIV-1-infected adults initiating treatment in resource-constrained countries: the antiretroviral therapy in low-income countries (ART-LINC) collaboration. *J Acquir Immune Defic Syndr* 2007; **45:** 52–59.

78 Rajasuriar R, Gouillou M, Spelman T, et al. Clinical predictors of immune reconstitution following combination antiretroviral therapy in patients from the Australian HIV Observational Database. *PLoS One* 2011; **6:** e20713.

79 Helleberg M, Kronborg G, Larsen CS, et al. Causes of death among Danish HIV patients compared with population controls in the period 1995–2008. *Infection* 2012; **40:** 627–34.

80 Abrams D, Lévy Y, Losso MH, et al, and the INSIGHT-ESPRIT Study Group, and the SILCAAT Scientific Committee. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med* 2009; **361:** 1548–59.

81 Sereti I, Dunham RM, Spritzler J, et al, and the ACTG 5214 Study Team. IL-7 administration drives T cell-cycle entry and expansion in HIV-1 infection. *Blood* 2009; **113:** 6304–14.

82 Vandergeeten C, Fromentin R, DaFonseca S, et al. Interleukin-7 promotes HIV persistence during antiretroviral therapy. *Blood* 2013; **121:** 4321–29.

83 Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA* 2012; **308:** 387–402.

84 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. June 2013. http://www.who.int/hiv/pub/guidelines/arv2013/download/en/index.html (accessed Aug 30, 2013).

85 Sigaloff KC, Hamers RL, Wallis CL, et al, and the PharmAccess African Studies to Evaluate Resistance (PASER). Unnecessary antiretroviral treatment switches and accumulation of HIV resistance mutations; two arguments for viral load monitoring in Africa. *J Acquir Immune Defic Syndr* 2011; **58:** 23–31.

86 Boyer S, March L, Kouanfack C, et al, and the Stratall ANRS 12110/ESTHER Study Group. Monitoring of HIV viral load, CD4 cell count, and clinical assessment versus clinical monitoring alone for antiretroviral therapy in low-resource settings (Stratall ANRS 12110/ESTHER): a cost-effectiveness analysis. *Lancet Infect Dis* 2013; **13:** 577–86.

87 Keiser O, Orrell C, Egger M, et al, and the Swiss HIV Cohort Study (SHCS) and the International Epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA). Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared. *PLoS Med* 2008; **5:** e148.

88 Boulle A, Schomaker M, May M, Egger M, Sterne JA. Mortality after starting ART in treatment-naïve adults in 3 continents: collaborative analysis of international epidemiologic databases to evaluate AIDS in southern Africa and ART cohort collaboration cohorts. 20th Conference on Retroviruses and Opportunistic Infections. Atlanta, Georgia; 2013.

89 Rodger AJ, Lodwick R, Schechter M, et al, and the INSIGHT SMART, ESPRIT Study Groups. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. *AIDS* 2013; **27:** 973–79.

90 Walker BD, Hirsch MS. Antiretroviral therapy in early HIV infection. *N Engl J Med* 2013; **368:** 279–81.

91 Sabin CA, Cooper DA, Collins S, Schechter M. Rating evidence in treatment guidelines: a case example of when to initiate combination antiretroviral therapy (cART) in HIV-positive asymptomatic persons. *AIDS* 2013; **27:** 1839–46.

92 Kulkarni SP, Shah KR, Sarma KV, Mahajan AP. Clinical uncertainties, health service challenges, and ethical complexities of HIV "test-and-treat": a systematic review. *Am J Public Health* 2013; **103:** e14–23.

93 Kranzer K, Govindasamy D, Ford N, Johnston V, Lawn SD. Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review. *J Int AIDS Soc* 2012; **15:** 17383.

94 Boulle A, Van Cutsem G, Hilderbrand K, et al. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. *AIDS* 2010; **24:** 563–72.

95 Centers for Disease Control and Prevention. Vital signs: HIV prevention through care and treatment – United States2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6047a4.htm (accessed June 3, 2014).

96 Gardner EM, Burman WJ, Steiner JF, Anderson PL, Bangsberg DR. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. *AIDS* 2009; **23:** 1035–46.

97 World Health Organization. WHO HIV drug resistance report 2012. 2012.

98 Lawn SD, Meintjes G. Pathogenesis and prevention of immune reconstitution disease during antiretroviral therapy. *Expert Rev Anti Infect Ther* 2011; **9:** 415–30.

99 Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M, and the IeDEA Southern and Central Africa. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10:** 251–61.

100 Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2010; **24:** 2381–90.

101 Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat Med* 1999; **5:** 512–17.

102 Chun TW, Nickle DC, Justement JS, et al. Persistence of HIV in gut-associated lymphoid tissue despite long-term antiretroviral therapy. *J Infect Dis* 2008; **197:** 714–20.

103 Cusini A, Vernazza PL, Yerly S, et al, and the Swiss HIV Cohort Study. Higher CNS penetration-effectiveness of long-term combination antiretroviral therapy is associated with better HIV-1 viral suppression in cerebrospinal fluid. *J Acquir Immune Defic Syndr* 2013; **62:** 28–35.

104 Saleh S, Solomon A, Wightman F, Xhilaga M, Cameron PU, Lewin SR. CCR7 ligands CCL19 and CCL21 increase permissiveness of resting memory CD4+ T cells to HIV-1 infection: a novel model of HIV-1 latency. *Blood* 2007; **110:** 4161–64.

105 Yang HC, Xing S, Shan L, et al. Small-molecule screening using a human primary cell model of HIV latency identifies compounds that reverse latency without cellular activation. *J Clin Invest* 2009; **119:** 3473–86.

106 Chomont N, El-Far M, Ancuta P, et al. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. *Nat Med* 2009; **15:** 893–900.

107 Wightman F, Solomon A, Khoury G, et al. Both CD31(+) and CD31 naive CD4(+) T cells are persistent HIV type 1-infected reservoirs in individuals receiving antiretroviral therapy. *J Infect Dis* 2010; **202:** 1738–48.

108 Ellery P, Sonza S, Paukovics G, et al. CD14lo/CD16hi monocytes are more permissive to HIV infection in vitro and may selectively harbour HIV-1 in patients on highly active antiretroviral therapy. 11th Conference on Retroviruses and Opportunistic Infections; 2004; San Francisco, CA; 2004. p. Abstract 426.

109 Gorry P, Purcell D, Howard J, McPhee D. Restricted HIV-1 infection of human astrocytes: potential role of nef in the regulation of virus replication. *J Neurovirol* 1998; **4:** 377–86.

110 Van Lint C, Bouchat S, Marcello A. HIV-1 transcription and latency: an update. *Retrovirology* 2013; **10:** 67.

111 Huang J, Wang F, Argyris E, et al. Cellular microRNAs contribute to HIV-1 latency in resting primary CD4+ T lymphocytes. *Nat Med* 2007; **13:** 1241–47.

112 Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N Engl J Med* 2009; **360:** 692–98.

113 Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med* 2013; **369:** 1828–35.

114 Yukl SA, Boritz E, Busch M, et al. Challenges in detecting HIV persistence during potentially curative interventions: a study of the Berlin patient. *PLoS Pathog* 2013; **9:** e1003347.

115 Li L, Krymskaya L, Wang J, et al. Genomic Editing of the HIV-1 Coreceptor CCR5 in Adult Hematopoietic Stem and Progenitor Cells Using Zinc Finger Nucleases. *Mol Ther JAm Soc Gene Ther* 2013; **21:** 1259–69.

116 Sáez-Cirión A, Bacchus C, Hocqueloux L, et al, and the ANRS VISCONTI Study Group. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. *PLoS Pathog* 2013; **9:** e1003211.

117 Lodi S, Meyer L, Kelleher AD, et al. Immunovirologic control 24 months after interruption of antiretroviral therapy initiated close to HIV seroconversion. *Arch Intern Med* 2012; **172:** 1252–55.

118 Ananworanich J, Schuetz A, Vandergeeten C, et al, and the RV254/SEARCH 010 Study Group. Impact of multi-targeted antiretroviral treatment on gut T cell depletion and HIV reservoir seeding during acute HIV infection. *PLoS One* 2012; **7:** e33948.

119 Lewin SR, Rouzioux C. HIV cure and eradication: how will we get from the laboratory to effective clinical trials? *AIDS* 2011; **25:** 885–97.

120 Archin NM, Liberty AL, Kashuba AD, et al. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. *Nature* 2012; **487:** 482–85.

121 Elliott J, Solomon A, Wightman F, et al. The Safety and Effect of Multiple Doses of Vorinostat on HIV Transcription in HIV+ Patients Receiving cART. 20th Conference on Retroviruses and Opportunistic Infections. Atlanta, GA; 2013. p. 50LB.

122 Shan L, Deng K, Shroff NS, et al. Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. *Immunity* 2012; **36:** 491–501.

123 Papagno L, Alter G, Assoumou L, et al, and the ORVACS Study Group. Comprehensive analysis of virus-specific T-cells provides clues for the failure of therapeutic immunization with ALVAC-HIV vaccine. *AIDS* 2011; **25:** 27–36.

124 Garcia F, Climent N, Guardo AC, et al. A dendritic cell-based vaccine elicits T cell responses associated with control of HIV-1 replication. *Science Transl Med* 2013; **5:** 166ra2.

125 Hansen SG, Piatak M Jr, Ventura AB, et al. Immune clearance of highly pathogenic SIV infection. *Nature* 2013; **502:** 100–04.

126 Dutta A, Wirtz AL, Baral S, Beyrer C, Cleghorn FR. Key harm reduction interventions and their impact on the reduction of risky behavior and HIV incidence among people who inject drugs in low-income and middle-income countries. *Curr Opin HIV AIDS* 2012; **7:** 362–68.

127 Kourtis AP, Lee FK, Abrams EJ, Jamieson DJ, Bulterys M. Mother-to-child transmission of HIV-1: timing and implications for prevention. *Lancet Infect Dis* 2006; **6:** 726–32.

128 Breastfeeding, Group HIVITS, Coutsoudis A, et al. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J Infect Dis* 2004; **189:** 2154–66.

129 de Vincenzi I, and the Kesho Bora Study Group. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis* 2011; **11:** 171–80.

130 Thior I, Lockman S, Smeaton LM, et al, and the Mashi Study Team. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. *JAMA* 2006; **296:** 794–805.

131 Coovadia HM, Brown ER, Fowler MG, et al, and the HPTN 046 protocol team. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; **379:** 221–28.

132 Thomas TK, Masaba R, Borkowf CB, et al, and the KiBS Study Team. Triple-antiretroviral prophylaxis to prevent mother-to-child HIV transmission through breastfeeding--the Kisumu Breastfeeding Study, Kenya: a clinical trial. *PLoS Med* 2011; **8:** e1001015.

133 Wettstein C, Mugglin C, Egger M, et al, and the IeDEA Southern Africa Collaboration. Missed opportunities to prevent mother-to-child-transmission: systematic review and meta-analysis. *AIDS* 2012; **26:** 2361–73.

134 Nachega JB, Uthman OA, Anderson J, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. *AIDS* 2012; **26:** 2039–52.

135 Cohen MS, Chen YQ, McCauley M, et al, and the HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365:** 493–505.

136 Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science* 2013; **339:** 966–71.

137 Coates T, Eshleman S, Chariyalertsak S, et al. Community-level reductions in estimated HIV incidence: HIV Prevention Trials Network 043, Project Accept. 20th Conference on Retroviruses and Opportunistic Infections (CROI). Atlanta, GA; 2013. p. Abstract 30.

138 Sabapathy K, Van den Bergh R, Fidler S, Hayes R, Ford N. Uptake of home-based voluntary HIV testing in sub-Saharan Africa: a systematic review and meta-analysis. *PLoS Med* 2012; **9:** e1001351.

139 Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis* 2011; **52:** 793–800.

140 Sood N, Wagner Z, Jaycocks A, Drabo E, Vardavas R. Test-and-treat in Los Angeles: a mathematical model of the effects of test-and-treat for the population of men who have sex with men in Los Angeles County. *Clin Infect Dis* 2013; **56:** 1789–96.

141 Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med* 2005; **2:** e298.

142 Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007; **369:** 643–56.

143 Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; **369:** 657–66.

144 Baeten JM, Donnell D, Ndase P, et al, and the Partners PrEP Study Team. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367:** 399–410.

145 Thigpen MC, Kebaabetswe PM, Paxton LA, et al, and the TDF2 Study Group. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* 2012; **367:** 423–34.

146 Choopanya K, Martin M, Suntharasamai P, et al, and the Bangkok Tenofovir Study Group. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2013; **381:** 2083–90.

147 Grant RM, Lama JR, Anderson PL, et al, and the iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363:** 2587–99.

148 Van Damme L, Corneli A, Ahmed K, et al, and the FEM-PrEP Study Group. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012; **367:** 411–22.

149 Marrazzo J, Ramjee G, Nair G, et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE study (MTN 003). 20th Conference on Retroviruses and Opportunistic Infections (CROI). Atlanta, GA; 2013. p. Abstract 26LB.

150 Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al, and the CAPRISA 004 Trial Group. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 2010; **329:** 1168–74.

151 Obiero J, Mwethera PG, Hussey GD, Wiysonge CS. Vaginal microbicides for reducing the risk of sexual acquisition of HIV infection in women: systematic review and meta-analysis. *BMC Infect Dis* 2012; **12:** 289.

152 Herrera C, Shattock RJ. Candidate Microbicides and Their Mechanisms of Action. *Curr Top Microbiol Immunol* 2013 [Epub ahead of print].

153 Ball C, Krogstad E, Chaowanachan T, Woodrow KA. Drug-eluting fibers for HIV-1 inhibition and contraception. *PLoS One* 2012; **7:** e49792.

154 Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. *Cochrane Database Syst Rev* 2009; **2:** CD003362.

155 Hallett TB, Alsallaq RA, Baeten JM, et al. Will circumcision provide even more protection from HIV to women and men? New estimates of the population impact of circumcision interventions. *Sex Transm Infect* 2011; **87:** 88–93.

156 Uthman OA, Popoola TA, Yahaya I, Uthman MM, Aremu O. The cost-utility analysis of adult male circumcision for prevention of heterosexual acquisition of HIV in men in sub-Saharan Africa: a probabilistic decision model. *Value Health* 2011; **14:** 70–79.

157 Ford N, Chu K, Mills EJ. Safety of task-shifting for male medical circumcision: a systematic review and meta-analysis. *AIDS* 2012; **26:** 559–66.

158 Gray RH, Wawer MJ, Kigozi G. Programme science research on medical male circumcision scale-up in sub-Saharan Africa. *Sex Transm Infect* 2013; **89:** 345–49.

159 Lorimer K, Kidd L, Lawrence M, McPherson K, Cayless S, Cornish F. Systematic review of reviews of behavioural HIV prevention interventions among men who have sex with men. *AIDS Care* 2013; **25:** 133–50.

160 Wariki WM, Ota E, Mori R, Koyanagi A, Hori N, Shibuya K. Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in low- and middle-income countries. *Cochrane Database Syst Rev* 2012; **2:** CD005272.

161 Kerrigan DL, Fonner VA, Stromdahl S, Kennedy CE. Community empowerment among female sex workers is an effective HIV prevention intervention: a systematic review of the peer-reviewed evidence from low- and middle-income countries. *AIDS Behav* 2013; **17:** 1926–40.

162 Kennedy CE, Medley AM, Sweat MD, O'Reilly KR. Behavioural interventions for HIV positive prevention in developing countries: a systematic review and meta-analysis. *Bull World Health Organ* 2010; **88:** 615–23.

163 Scott-Sheldon LA, Huedo-Medina TB, Warren MR, Johnson BT, Carey MP. Efficacy of behavioral interventions to increase condom use and reduce sexually transmitted infections: a meta-analysis, 1991 to 2010. *J Acquir Immune Defic Syndr* 2011; **58:** 489–98.

164 Fonner VA, Denison J, Kennedy CE, O'Reilly K, Sweat M. Voluntary counseling and testing (VCT) for changing HIV-related risk behavior in developing countries. *Cochrane Database Syst Rev* 2012; **9:** CD001224.

165 Barnabas RV, Celum C. Infectious co-factors in HIV-1 transmission herpes simplex virus type-2 and HIV-1: new insights and interventions. *Curr HIV Res* 2012; **10:** 228–37.

166 Celum C, Wald A, Lingappa JR, et al, and the Partners in Prevention HSV/HIV Transmission Study Team. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med* 2010; **362:** 427–39.

167 Lingappa JR, Baeten JM, Wald A, et al, and the Partners in Prevention HSV/HIV Transmission Study Team. Daily acyclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial. *Lancet* 2010; **375:** 824–33.

168 Mugwanya K, Baeten JM, Mugo NR, Irungu E, Ngure K, Celum C. High-dose valacyclovir HSV-2 suppression results in greater reduction in plasma HIV-1 levels compared with standard dose acyclovir among HIV-1/HSV-2 coinfected persons: a randomized, crossover trial. *J Infect Dis* 2011; **204:** 1912–17.

169 Barnabas RV, Webb EL, Weiss HA, Wasserheit JN. The role of coinfections in HIV epidemic trajectory and positive prevention: a systematic review and meta-analysis. *AIDS* 2011; **25:** 1559–73.

170 Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995; **346:** 530–36.

171 Ng BE, Butler LM, Horvath T, Rutherford GW. Population-based biomedical sexually transmitted infection control interventions for reducing HIV infection. *Cochrane Database Syst Rev* 2011; **3:** CD001220.

172 Buchbinder SP, Mehrotra DV, Duerr A, et al, and the Step Study Protocol Team. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet* 2008; **372:** 1881–93.

173 Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al, and the MOPH-TAVEG Investigators. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009; **361:** 2209–20.

174 Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. *N Engl J Med* 2012; **366:** 1275–86.

175 Haynes BF, McElrath MJ. Progress in HIV-1 vaccine development. *Curr Opin HIV AIDS* 2013; **8:** 326–32.