Update on 2004 Background Paper
Written by Warren Kaplan

Background Paper 6.7
Human Immunodeficiency Virus (HIV)/
Acquired Immune Deficiency Syndromes (AIDS)

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What is new since 2004?

Treatment as prevention.
There is increasingly strong scientific evidence for use of antiretrovirals (ARV) in the prevention of HIV transmission. HIV transmission only occurs from people with HIV, and the greatest risk factor for HIV transmission is the viral load and lowering the viral load reduces the risk of transmission.1 ARV therapy dramatically lowers viral load and numerous observational studies have demonstrated its potential for prevention of HIV transmission.2,3

The so-called HPTN 052 Trial clearly demonstrated the effectiveness of treatment as prevention. The early initiation of antiretroviral therapy reduced rates of sexual transmission of HIV-1 and clinical events, indicating both personal and public health benefits from such therapy.4

Prevention of maternal-to-child transmission (PMTCT) offers further proof of concept that ARV therapy essentially interrupts HIV transmission. In the USA and Europe, perinatal AIDS cases have been virtually eliminated most likely due to the implementation of guidelines for the universal counseling, voluntary HIV testing and ARVs for pregnant women and newborn infants.5 In 2008, the majority of the 430 000 new paediatric HIV infections were in sub-Saharan Africa, where there is recent evidence that ARVs can be used to decrease transmission to 1%.1

Improvement in 2nd and 3rd line therapeutics (e.g. approval of integrase inhibitors, CCR5 inhibitors new Protease inhibitors and NNRTs). See Section 3.2, below

The rise and fall of treatment sparing/episodic regimens.
The inherent risks and problems associated with lifelong antiretroviral therapy have led to studies of treatment-sparing strategies that might provide the benefits of antiretroviral therapy while minimizing the risk of adverse events and other risks associated with long-term use. The SMART trial showed that episodic antiretroviral therapy guided by the CD4+ count significantly increased the risk of opportunistic disease or death from any cause, as compared with continuous antiretroviral therapy, largely as a consequence of lowering the CD4+ cell count and increasing the viral load. Episodic antiretroviral therapy does not reduce the risk of adverse events that have been associated with antiretroviral therapy.6

Treating patients earlier as illustrated in various guidelines, to counter the effects of non AIDS-related morbidities.
Key guidelines are now recommending treatment for all adults with HIV infection; the strength of the recommendation and the quality of the evidence increase with decreasing CD4+ cell count and the presence of certain concurrent conditions. 7

In brief, recommended initial regimens include two nucleoside reverse transcriptase inhibitors (tenofovir/emtricitabine or abacavir/ lamivudine) plus a non-nucleoside reverse transcriptase inhibitor (efavirenz), a ritonavir-boosted protease inhibitor (atazanavir or darunavir), or an integrase strand transfer inhibitor (raltegravir).8 Alternatives in each class
are recommended for patients with or at risk of certain concurrent conditions. CD4+ cell count and HIV-1 RNA level should be monitored, as should engagement in care, ART adherence, HIV drug resistance, and quality-of-care indicators. Confirmed treatment failure should be addressed promptly and multiple factors considered.

Pre-exposure prophylaxis (PrEP):
Taking a daily pill to reduce HIV risk is a potential breakthrough pharmaceutical prevention strategy. Daily use of some antiretrovirals (Truvada®; Gilead) has shown up to 73% effective in preventing HIV/AIDS transmission among men who have sex with men (MSM). 9

Vaginal microbicides:
There have been setbacks in the development of a gel containing tenofovir— a microbicide that can be used vaginally or anally to prevent HIV transmission. The CAPRISA study, unveiled to much fanfare in 2010, found such a gel partially prevented infection in women.10 But this year, another study was partly cancelled after researchers discovered that one of the gels it was testing failed to prevent infection. Scientists are unsure why the latest trial was unsuccessful.

Several microbicide candidates are under study. Following several failures in Phase II/III trials (PRO 2000, BufferGel and VivaGel), new candidates using active ingredients from ARVs have shown promising results in Phase II trials. These include dapivirine gel, a long acting dapivirine-based microbicide ring, and CAPRISA 004 tenofovir-gel, which is currently being fast-tracked by the FDA pending results of confirmatory trials.11

Global Progress
The most recent study in 2012 by the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that new HIV infections and AIDS-related deaths have fallen to the lowest levels since the peak of the epidemic. See Appendix 6.7.1 and Appendix 6.7.2.

Briefly, in the last ten years the landscape of national HIV epidemics has changed for the better in most countries, especially in sub-Saharan Africa. There were 700 000 fewer new HIV infections across the world in 2011 than in 2001. Latest data show that a 50% reduction in the rate of new HIV infections (HIV incidence) has been achieved in 25 low- and middle-income countries between 2001 and 2011.

However, in the Middle East and North Africa, the number of people newly infected with HIV increased by 35% between 2001 and 2011, and the rate of new HIV infections continues to rise in Eastern Europe and Central Asia.

The commercial market for antiviral therapeutics will ensure that there will be no shortage of private research funding for the immediate future. Opportunities exist for public funding of research. Both private and public funders, however, should consider the following:
- Although the clinical efficacy with the existing antivirals has improved dramatically, additional forms of therapy and treatment strategies are needed.
- Antiviral therapy alone will not end the epidemic and a comprehensive public health approach remains essential.
Because the HIV genome mutates very rapidly, during the course of an infection, the development of resistance to antivirals is common. There is a continuing need for the development of new antiviral agents.
1. **Introduction**

AIDS is the deadliest epidemic of our time. The infective agent, human immunodeficiency virus (HIV), has already infected more than 60 million people around the world. AIDS is the leading cause of infectious disease mortality, surpassing tuberculosis and malaria. In 2008, about 68% of people living with HIV were in sub-Saharan Africa with around 35% in eight countries alone. In 2005 and 2009, the G8 met in Scotland and Italy and committed to achieving universal access to HIV prevention, care and treatment by 2010. However, universal access remains a dream for millions of people and faces serious technical, economic and political challenges on a number of fronts. See Appendices 6.7.1-4.

2. **What are the Epidemiological Trends for Europe and the World?**

2.1 **Western and Central Europe**

At the end of 2010 it was estimated that around 840 000 people were living with HIV in Western and Central Europe. See also Appendix 6.7.5.

The HIV epidemic is fairly stable as a whole, with the transmission rate having changed little since 2004. See Appendix 6.7.1. Although the total number of people living with HIV and AIDS in the European region is relatively small when compared to areas such as Asia and sub-Saharan Africa, HIV and AIDS in Western and Central Europe is still considered to be a major public health issue. See Appendix 6.7.5: WHO (2010) 'European Action Plan for HIV/AIDS 2012-2015' and Appendix 6.7.6: WHO Europe (2009, December) 'HIV/AIDS surveillance in Europe 2008'.

More encouragingly, the total deaths due to AIDS in this region have decreased since the introduction of combination antiretroviral treatment in the mid-1990s (See also Figure 6.7.2). Most Western and Central European countries benefit from wealthy economies, stable infrastructures and developed healthcare systems, and so the majority of people needing antiretroviral treatment are receiving it. Many people now consider HIV as a chronic disease. Generally HIV and AIDS have affected Western Europe more than Central Europe. See Figure 6.7.1. At an estimated 0.6%, Portugal has the highest HIV prevalence, followed by Switzerland, Spain and France. See also Appendix 6.7.1. In 2010 the UK reported the highest number of new HIV diagnoses, where incidence had increased by more than 50% between 2000 and 2009. (See Appendix 6.7.6).

HIV prevalence in Central Europe has remained at a relatively low level (see Figure 6.7.1). Croatia, Slovakia and Slovenia all have HIV prevalence figures under 0.1% (see also Appendix 6.7.1 and Appendix 6.7.6). Generally in the region key populations at higher risk include injecting drug users (IDUs) and their sexual partners, men who have sex with men (MSM), transgender people, prisoners, sex workers and migrants (see Appendix 6.7.5). In Western Europe the epidemic is homogenized, with heterosexual transmission accounting for 40% of diagnoses, many of which are among people who became infected in regions where there is a generalized epidemic.
In both Western and Central Europe, injecting drug use (IDU) accounted for 4% of new HIV diagnoses in 2010. There has been a steady decline in new HIV infections among injecting drug users in Western and Central Europe since the beginning of the century, which could be explained by the increasing availability of harm reduction measures, such as needle exchanges. IDU is still an important factor in several countries, and there have been some large increases in particular localized areas (see Appendix 6.7.7). Poland has reached an HIV prevalence of 18% in some areas among IDUs, and in Greece and Romania there have been significant increases in cases of HIV among this group. See also Appendix 6.7.8.

Figure 6.7.1 below shows the estimated adult HIV prevalence in 2009.

With the roll-out of anti-retrovirals (ARVs) there was a general expectation that the widespread availability of antiretroviral therapy would act as an incentive for individuals to get tested for HIV. Once diagnosed, the drugs will help them stay healthy for a longer period of time. However, in Western and Central Europe, rates of late diagnosis have either remained at high levels or have increased. Unfortunately, definitions of “diagnosing late” vary from less than 50 to less than 200 CD4+ T cells/microliter. Even now, many people are unaware that they are living with HIV. Opportunities to diagnose HIV infections are often missed, particularly in healthcare settings, and testing among injecting drug users is
particularly low. Late diagnosis of HIV has serious implications for both the individual and public health. Even considering that treatment reduces transmission rates, if a person is diagnosed at a late stage they are more likely to develop an AIDS-related illness, are less likely to respond to antiretroviral treatment and are at an increased risk of mortality. As people are more likely to take precautions to prevent transmission if they know they are infected with the virus, late or no diagnosis can increase the risk that HIV will be transmitted, which has wider public health implications.

In sum, reasons why people in Western and Central Europe still die from AIDS include:

- **A high number of late diagnoses.**
  Early diagnosis of HIV infection is essential to ensuring that patients are referred promptly for evaluation, provided treatment (if indicated), and linked into counseling and related support services to help them reduce their risk for transmitting HIV to others. Diagnosing persons during acute infection is particularly important. It is during this phase that HIV-infected persons are most infectious, but test negative for HIV antibodies and therefore unknowingly continue to engage in those high-risk behaviors associated with HIV transmission. A key point for emphasis therefore is the need to diagnose all persons with HIV. There is a critical need to encourage wider uptake of voluntary testing for HIV to ensure earlier access to counselling and treatment (as needed). It would appear that testing uptake increases with ‘opt-out’ policies – whereby a test is performed unless the patient asks not to have one.

- **Access to treatment and care for migrants may be limited.**
  There is some evidence that in some European countries, migrants from countries with generalized HIV epidemics are disproportionally affected by HIV and do not access testing or treatment services as readily as other populations.

- **Drug resistance.**

- **Ageing and disease progression.**
  The prevalence of human immunodeficiency virus (HIV) in the over-50 age group is increasing as a consequence of younger adults ageing with HIV, in addition to new diagnoses in later life. Older adults are vulnerable to late or missed diagnosis and poorer treatment outcomes, due to the misconception that they are not at risk. As the HIV population ages, the emergence of disease and treatment complications such as cardiovascular disease, osteoporosis and dementia are evident. Renal function declines with age and HIV infection, affecting drug clearance – the risk of drug toxicities and mortality associated with cardiovascular events. Management of older adults with HIV and multiple comorbidities presents challenges to infectious diseases physicians and geriatricians alike. Inclusion of older adults in future HIV clinical trials will help design healthcare models to provide for this growing population.

### 2.2 Eastern Europe

Driving the epidemics in Eastern Europe is unprotected sex (including between men) and sharing contaminated drug-injecting equipment. See also Appendix 6.7.1. The HIV incidence among people who inject drugs in St Petersburg, Russian Federation, for example, was 8.1 per 100 person-years in 2009, almost twice the rate five years earlier. Appendix 6.7.1. By some estimates, there could be as many as 3 million injecting drug users in the Russian Federation alone, more than 600 000 in Ukraine and up to 200 000 in Kazakhstan. In Estonia and Latvia, it has been estimated that up to 1% of the adult population injects illicit drugs,
while, in Kyrgyzstan, that figure could approach 2%. Most of these drug users are male and many are very young. In St Petersburg, studies found that 30% of males were under 19 years of age, while in Ukraine 20% were still in their teens. The situation regarding HIV in IDUs in Eastern Europe is worrying. Data on reported HIV cases in IDUs suggest increasing incidence of HIV infection among people who inject drugs. In 2007, IDUs accounted for 57% of newly diagnosed HIV infections reported in this region.

The prevalence of HIV infection among adults in 2009 was 1% [0.9–1.2%] in the Russian Federation and 1.1% [1.0–1.3%] in Ukraine. See Appendix 6.7.1. Together, those countries account for almost 90% of the people newly reported to be diagnosed with HIV infection in this region and are home to twice as many people living with HIV as all of Western and Central Europe combined. See Appendix 6.7.1. Unlike most other regions, the number of people dying from AIDS-related causes continues to rise in Eastern Europe and Central Asia. The HIV epidemic claimed an estimated 83 000 [69 000–100 000] lives from AIDS-related causes in 2010, which is 11 times more than the estimated 7800 [6000–11 000] in 2001. See Appendix 6.7.1.

Since the mid-1990s, there has been a significant decline in AIDS-related mortality in Western and Central Europe (“EU27” and “EU15”). Most people living with HIV in these regions have access to combination therapy. As Figure 6.7.2 illustrates, the rate of HIV/AIDS deaths (per 100 000) has dramatically dropped in the EU27 and EU 15 due to the widespread availability of antiretroviral treatment beginning in the mid-late 1990s. In the EU12, HIV/AIDS is driven primarily by injecting drug use and the mortality changes are due to programmes that reach injecting drug users, including those in prisons and those who belong to marginalized minorities. See Appendix 6.7.1.

Figure 6.7.2: Standardized death rates (per 100 000 persons) of HIV/AIDS among country-components of the European Union
2.2 The World (including Europe)

The most recent 2012 UNAIDS report, *Together We Will End AIDS* (Appendix 6.7.1) shows a more than 50% reduction in the rate of new HIV infections has been achieved across 25 low- and middle-income countries most affected by HIV. In some of the countries which have the highest HIV prevalence in the world, rates of new HIV infections have been cut dramatically since 2001 due to increased access to medicines and improved healthcare delivery; by 73% in Malawi, 71% in Botswana, 68% in Namibia, 58% in Zambia, 50% in Zimbabwe and 41% in South Africa and Swaziland.

Sub-Saharan Africa increased the number of people on antiretroviral treatment by 59% in the last two years alone. The available evidence in the Middle East and North Africa points to ongoing increases in the number of people acquiring HIV infection. In this region in 2011, an estimated 36 000 [26 000–56 000] adults acquired HIV infection, 29% more than in 2001.
More specifically, the number of people dying annually from AIDS-related causes worldwide decreased from a peak of 2.3 million [2.1 million–2.5 million] in 2005 to an estimated 1.7 million [1.6 million–2.0 million] in 2011. This is most evident in sub-Saharan Africa, where an estimated 550 000 (31%) fewer people died from AIDS-related causes in 2011 than in 2005, when the number of AIDS-related deaths peaked. AIDS-related deaths in the Middle East and North Africa increased from 14 000 [8600–28 000] in 2001 to 25 000 [17 000–35 000] in 2011. See Appendix 6.7.1.

In Latin America, wide access to antiretroviral therapy has helped reduce the annual number of people dying from AIDS-related causes to 57 000 [35 000–86 000] in 2011, down from 63 000 [35 000–105 000] 10 years earlier. In the Caribbean, an estimated 10 000 [8000–12 000] people died from AIDS-related causes in 2011, about half as many as in 2001.

In Western and Central Europe and North America, the extensive availability of antiretroviral therapy, especially in the countries with the largest epidemics, has significantly reduced AIDS-related mortality. The combined number of people dying from AIDS-related causes in these regions has varied little during the past decade and totalled an estimated 29 000 [26 000–36 000] in 2011. However, the report shows that HIV continues to have a disproportionate impact on sex workers, men who have sex with men and people who inject drugs. HIV prevention and treatment programmes are largely failing to reach these key populations.

The number of people dying from AIDS-related causes has remained stable in Asia (about 330 000 [260 000–420 000] persons in 2011), the largest number of deaths outside of sub-Saharan Africa. In Eastern Europe and Central Asia, AIDS-related deaths continue to rise. In 2011, an estimated 90 000 [74 000–110 000] people died of AIDS-related causes, six times more than the estimated 15 000 [11 000–26 000] in 2001. In the Russian Federation alone, the number of people reported newly diagnosed increased from 39 207 in 2005 to 62 581 in 2010. Since 2005, newly reported HIV cases have also been increasing in the smaller epidemics in Central Asia (Kyrgyzstan, Tajikistan and Uzbekistan). The use of contaminated injecting equipment remains the main route of transmission in this region.

HIV-related tuberculosis (TB) remains a serious challenge as TB remains the leading cause of death among people living with HIV. More than 80% of the people living with HIV and TB are in sub-Saharan Africa. Appendix 6.7.1.

Table 6.7.1 is taken from Appendix 6.7.9 (2011 UNAIDS report) and while slightly different than the numbers cited above (Appendix 6.7.1) they do show the order of magnitude changes in these metrics over time.
Table 6.7.1: Various measures of HIV/AIDS burden of disease since 2001

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2005</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>People living with HIV</td>
<td>28.6 million</td>
<td>31.0 million</td>
<td>32.3 million</td>
<td>32.9 million</td>
<td>34 million</td>
</tr>
<tr>
<td></td>
<td>[26.7-30.9]</td>
<td>[29.2-32.7]</td>
<td>[30.4-33.8]</td>
<td>[31.0-34.4]</td>
<td>[31.6-35.2]</td>
</tr>
<tr>
<td>New HIV infections</td>
<td>3.15 million</td>
<td>2.81 million</td>
<td>2.74 million</td>
<td>2.72 million</td>
<td>2.67 million</td>
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<td>[2.96-3.33]</td>
<td>[2.63-2.97]</td>
<td>[2.52-2.93]</td>
<td>[2.48-2.93]</td>
<td>[2.46-2.90]</td>
</tr>
<tr>
<td>AIDS-related deaths</td>
<td>1.85 million</td>
<td>2.22 million</td>
<td>2.04 million</td>
<td>1.89 million</td>
<td>1.76 million</td>
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<td></td>
<td>[1.67-2.16]</td>
<td>[2.07-2.48]</td>
<td>[1.87-2.21]</td>
<td>[1.72-2.05]</td>
<td>[1.59-1.91]</td>
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<tr>
<td>New infections in children</td>
<td>550 000 [490 000-620 000]</td>
<td>540 000 [480 000-600 000]</td>
<td>460 000 [400 000-510 000]</td>
<td>430 000 [370 000-490 000]</td>
<td>390 000 [340 000-450 000]</td>
</tr>
</tbody>
</table>

Source: Appendix 6.7.9: 2011 UNAIDS report

3. What is the Control Strategy? Is There an Effective Package of Control Methods Assembled into a “Control Strategy” for Most Epidemiological Settings?

3.1 Is there a pharmaceutical ‘gap’?

Yes, there is a gap because there is no cure for HIV. Further, the presence of continued resistance demands more therapeutic options going forward and this constitutes a “gap” as well. Notwithstanding the many treatments that are clinically efficacious, operationally effective and prolong life. (See Section 3.2), prevention of resistance is a priority that requires unrelenting patient education regarding the risks of resistance and the use of improved drug regimens that ensure optimal tolerance, adherence, and potency. Third, although the HIV intra-cell life cycle is well known, there need to be more therapeutics that attack all aspects of its life cycle.

3.2 Treatment options and targets

3.2.1 Viral life cycle

Whereas the HIV-1 life cycle presents many potential opportunities for therapeutic intervention, only a few have been exploited. The replication scheme of HIV-1, shown in Figure 6.7.6 (see page 42) (taken from Moore and Stevenson, 2000), marked with the steps blocked by approved inhibitors as of 2012 (numbers in panel 2A). A timing of the retroviral lifecycle is described in panel B based on the specific time window of inhibition by a specific drug class. In panel 2C, the inhibitors in development (normal text) or FDA approved (italic/bold text) are listed by inhibition of a specific retroviral replication event.

Attempts to block HIV-1 infection attack many steps in the viral life cycle of HIV-1. These steps include virus–cell attachment, virus entry and virus uncoating. The reverse transcription of viral cDNA, nuclear import and integration into the host cell's genome are
also potential sites of inhibition. One antagonist of viral entry (e.g. fusion inhibitors) has been approved by the FDA (Table 6.7.2) and others are now in, or approaching, human clinical trials. Fusion inhibitors are directed against both the viral glycoproteins that interact with receptors and co-receptors on the host cell membrane. The co-receptors CCR5 is also now a target for an approved medicine.

The design of post-entry inhibitors remains problematic; the more advanced inhibitors include agonists of the integrase enzyme, which mediates viral cDNA integration into the host cell’s genome. Design of new viral-entry inhibitors also considers the escape pathways adopted by the evolving HIV-1 virus in response to inhibition of its normal entry route. The most successful therapeutic approach will likely be a 'cocktail' of inhibitors, which block infection at several points, including the potential escape pathways.26

Specifically, the first step in the HIV-1 replication cycle, viral entry is the target for several classes of antiretroviral agents: attachment inhibitors, chemokine receptor antagonists, and fusion inhibitors. The HIV-1 envelope gp120/gp41 has affinity for the CD4 receptor and directs HIV-1 to CD4+ immune cells.27,28 Interaction of the gp120 subunit of the HIV-1 envelope with CD4 is followed by binding to an additional co-receptor, either the CC chemokine receptor CCR5 or the CXC chemokine receptor CXCR4. These sequential receptor-binding events trigger conformational changes in the HIV-1 envelope, exposing a hydrophobic domain on gp41 that mediates fusion with the cellular membrane. The entire entry process is completed within 1 h of virus contact with the cell (Fig. 2B). Gp120 and CD4 are targets for attachment inhibitors BMS-626529,27 which binds to the HIV-1 gp-120 envelope protein and prevents it from attachment to CD4 receptors and TNX-355, each of which have shown some clinical promise. TNX-355 (Ibalizumab) is a humanized anti-CD4 monoclonal antibody that binds to CD4 and inhibits HIV-1 envelope docking, but does not inhibit CD4 function in immunological context. It has not yet been evaluated by the U.S. Food and Drug Administration (FDA). Gp41 and the co-receptor CCR5 are the targets for the two approved entry agents: the peptide-based fusion inhibitor, fuzeon, and the small-molecule CCR5 chemokine receptor antagonist, maraviroc. See Section below.

In constructing an antiretroviral therapy (ART) regimen for a patient the treating clinician now has nearly 30 separate medicines in different classes as well as a variety of fixed dose combination pills to choose from – a remarkable diversification in just 25 years since the introduction of AZT for the treatment of HIV.28 See Table 6.7.2.

For the first time in over a decade a new class drug – the integrase inhibitor raltegravir – has now been added to the preferred choices for first line ART to be used in combination TDF/FTC.29 The preferred nucleoside/nucleotide “backbone” for NNRTI, boosted PI regimens and raltegravir has been narrowed to a single choice – that of TDF/FTC because of toxicity concerns associated with the other choices. In particular thymidine analogs – zidovudine (AZT) and stavudine (D4T) are no longer part of the preferred list because of the increased risk of lipoatrophy and other metabolic complications associated with long-term use. Dideoxyinosine (ddI) specifically in combination with tenofovir as a nucleoside backbone is generally not recommended due to toxicity considerations.30 See also Table 6.7.3

Table 6.7.2 is a list of all approved anti-HIV medicines in the USA. Some, but by no means all of these, include both adult and paediatric dosages. See AIDSinfo Drug Database http://aidsinfo.nih.gov/drugs/search/searchterm/0/1/
Table 6.7.2: List of all approved anti-HIV medicines in the USA

<table>
<thead>
<tr>
<th>Medicine</th>
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<tbody>
<tr>
<td>Abacavir</td>
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<tr>
<td>Abacavir / Lamivudine</td>
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<tr>
<td>Abacavir / Lamivudine / Zidovudine</td>
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<tr>
<td>Acyclovir</td>
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<td>Atazanavir</td>
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<td>Darunavir</td>
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<td>Delavirdine</td>
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<td>Didanosine</td>
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<tr>
<td>Efavirenz</td>
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<tr>
<td>Efavirenz / Emtricitabine / Tenofovir Disoproxil Fumarate</td>
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<tr>
<td>Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate</td>
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<tr>
<td>Emtricitabine</td>
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<tr>
<td>Emtricitabine / Rilpivirine / Tenofovir Disoproxil Fumarate</td>
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<td>Emtricitabine / Tenofovir Disoproxil Fumarate</td>
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<td>Enfuvirtide</td>
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<td>Fosamprenavir</td>
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<td>Indinavir</td>
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<td>Lamivudine</td>
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<td>Lopinavir / Ritonavir</td>
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<td>Maraviroc</td>
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<td>Nevirapine</td>
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<td>Raltegravir</td>
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<td>Stavudine</td>
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<tr>
<td>Tenofovir Disoproxil Fumarate</td>
</tr>
<tr>
<td>Tipranavir</td>
</tr>
<tr>
<td>Zidovudine</td>
</tr>
</tbody>
</table>


### 3.3 Treatment strategies

#### 3.3.1 SMART trial and progeny

The inherent risks and problems associated with lifelong antiretroviral therapy have led to the study of treatment-sparing strategies that might provide the benefits of antiretroviral therapy while minimizing the risk of adverse events and other risks associated with long-term use.

The SMART trial compared a control strategy, consistent with the 2003 guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents, in which available antiretroviral regimens were used in an uninterrupted manner with the goal of maximal and
The experimental drug conservation strategy entailed the episodic use of antiretroviral therapy according to CD4+ count thresholds: the use of antiretroviral therapy was deferred until the CD4+ count decreased to less than 250 cells per cubic millimeter, at which time antiretroviral therapy was to be initiated (or reinitiated) and continued until the CD4+ count increased to more than 350 cells per cubic millimeter. Total enrollment was 5472 persons in 33 countries and 318 sites. See http://pag.aids2012.org/session.aspx?s=124#2.

Trial enrollment was stopped because those patients receiving episodic therapy had twice the risk of disease progression (the development of clinical AIDS or death), the major outcome of the study. That is, episodic antiretroviral therapy guided by the CD4+ count significantly increased the risk of opportunistic disease or death from any cause, as compared with continuous antiretroviral therapy, largely as a consequence of lowering the CD4+ cell count and increasing the viral load. Episodic antiretroviral therapy did not reduce the risk of adverse events that have been associated with antiretroviral therapy.

Results of SMART established a new research agenda. The HIV treatment agenda includes research aimed at understanding the effects of untreated HIV on serious non-AIDS (SNA) diseases; studies of novel inflammatory and coagulation markers as predictors of SNA conditions; studies of new treatments for people with HIV to reduce inflammation and eliminate possible causes of inflammation; comparisons with non-HIV populations to understand the effects of HIV and HIV treatments on accelerated aging; genetic studies of SNA risk and of elevated biomarker levels; and a large clinical trial on when to start ART (the START trial). Overall, SMART provides an appreciation of the role of non-AIDS related mortality and morbidity in patients with HIV.

The START Trial:

See START trial (Strategic Timing of Antiretroviral Treatment) (http://www.niaid.nih.gov/volunteer/hivandinfectious/hivstudies/Pages/STARTStudy.aspx) (http://clinicaltrials.gov/ct2/show/NCT00867048)

The consensus is that continued substantial viral transmission remains the key stumbling block in overcoming the HIV pandemic and that initiation of ART makes persons less infectious. Generally, therapy is of net health benefit to HIV+ persons with HIV-related symptoms or with CD4<350 cells/µL.

The 2010 WHO Guidelines (http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf) assert that all adolescents and adults including pregnant women with HIV infection
and CD4 counts of ≤350 cells/mm³, should start ART, regardless of the presence or absence of clinical symptoms. The controversy is whether anti-retroviral therapy is of net health benefit to the asymptomatic HIV-positive person if started at a CD4 count >350 cells/µL (i.e. early ART).

As of January 2013, the START study is still recruiting but its objectives are to find out if the chance of developing a serious non-AIDS illness or of getting AIDS is less if patients start taking HIV medicines at a time when their CD4+ T cell count is still fairly high, instead of waiting until the CD4+ count is at the level where the evidence is good for starting treatment (< 350 cells/µL). The primary outcome is a composite endpoint: AIDS, serious non-AIDS diagnoses, and all-cause mortality.

The experimental arm is early ART in which patients are to be initiated on ARTs immediately following randomization using any licensed antiretroviral medication, in accordance with national treatment guidelines. The active comparator arm is the deferred ART protocol in which ART is held off until the CD4+ count declines to <350 cells/µL or AIDS develops.

3.3.2 Paediatric HIV: treatments, guidelines and dosage forms

There is still a major gap between children and adults in coverage of antiretroviral therapy. Globally, about 562 000 children received antiretroviral therapy in 2011 (up from 456 000 in 2010), but coverage was only 28% [25–32%]: higher than the 22% [20–25%] in 2010 but much lower than the 57% [53–60%] coverage of antiretroviral therapy among adults. Even though antiretroviral therapy services still reach only a small fraction of eligible children, substantially fewer children are dying from AIDS-related causes: 230 000 [200 000–270 000] in 2011 versus 320 000 [290 000–370 000] in 2005. See Appendix 6.7.1.

In part, this is due to the fact that the cumulative number of new HIV infections averted among children more than doubled between 2009 and 2011 in low- and middle-income countries, as services to eliminate new HIV infections among children were expanded (see Appendix 6.7.1). Almost 600 000 new HIV infections among children have been averted since 1995 due to the availability of antiretroviral prophylaxis both for pregnant women living with HIV and for their infants. Most of the children involved live in sub-Saharan Africa.

Globally, the majority of children with HIV are infected at the time of birth or shortly thereafter when they have limited immune function and an immature central nervous system. Infancy and early childhood is therefore a period of extreme vulnerability, and HIV infection in these first days or weeks of life can lead to rapid disease progression that can be sudden and deadly. To illustrate this, two-thirds of the deaths among infants enrolled in the deferred treatment arm of the South African Children With HIV Early Antiretroviral Therapy (CHER) study occurred before the age of 26 weeks. 32

Many of these children died suddenly of common childhood illnesses with what was considered, at the time, a “normal” or “safe” CD4 cell count. Contrast this with the natural history of HIV in adults, who can survive for many years without symptoms and in whom CD4 cell counts are highly predictive of disease progression. In recognition of the aggressiveness of HIV infection in infants and young children, national and international guidelines have now moved to recommend universal treatment of all children with
confirmed HIV infection younger than the age of 12 months regardless of clinical stage or CD4 cell count. See for example, reference 33.

It is essential to identify and treat HIV-infected children in infancy before the virus causes irreparable harm. Unfortunately, the diagnosis of HIV infection in young infants remains a challenge. The passive transfer of maternal antibodies confounds the diagnosis in children less than 18 months of age when they are most vulnerable. While expansion of early infant diagnosis programs utilizing dried blood spot systems has allowed for the identification of HIV infected infants even in remote settings, this requires the participation of antenatal and obstetrical services to first identify HIV-positive mothers and the subsequent follow-up of infants to test them at the appropriate time.

In settings such as sub-Saharan Africa where the prevalence of HIV is high, significant resources are needed to ensure universal antenatal HIV testing, training all healthcare workers in the management of HIV diagnosis and treatment, and integrating HIV care and treatment into the overall healthcare system. Routine testing at entry points to care such as immunization clinics or inpatient wards is very effective in identifying HIV-exposed and HIV-infected children in countries such as South Africa and Zambia.

The development of paediatric dosage forms has lagged behind the corresponding development for adults. A list of approved paediatric HIV medicines in the USA can be found at: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118951.htm and the most recent dosing chart from the CDC is at http://www.cdc.gov/globalaids/resources/pmtct-care/pmtct-pediatric-dosing-guide.html. See also Appendix 6.7.10.


The Paediatric European Network for the Treatment of AIDS (PENTA: http://www.pentatrials.org/) was established in 1991 as a collaboration between paediatric HIV centres in Europe. Trials are principally funded by the European Commission, by governmental bodies in a number of European countries and by support from the pharmaceutical industry. PENTA has guidelines of their own (as of 2009) intended for treating children with HIV in Europe, available on their website. http://www.pentatrials.org/HIV_759.pdf.

It is worth noting that PENTA wrote a letter to the WHO (See at http://www.pentatrials.org/PENTA%20letter%20re%20WHO%20jul%202010.pdf) asserting that the 2010 WHO guidance for children between age 1 and 5 are based on programmatic considerations, in particular as there is generally an inability to closely monitor a child clinically and by repeat CD4 count measurement if they are not started on antiretroviral therapy. PENTA noted that this kind of monitoring is available routinely in Europe and that “the evidence basis for these [WHO] recommendations is weak or very weak”.
3.3.3 Pre-exposure prophylaxis

This is an HIV prevention method in which people who do not have HIV, take a daily pill to reduce their risk of becoming infected. When used consistently, PrEP has been shown to be effective in men who have sex with men (MSM) and heterosexually-active men and women. In November 2010, the National Institutes of Health (NIH) announced the results of the iPrEx clinical trial, a large, multicountry research study examining PrEP among men having sex with men (MSM). Among MSM with detectable levels of the medication in their blood, the risk of HIV acquisition was reduced by more than 90%.38

In July 2011, the TDF2 study conducted in partnership with the Botswana Ministry of Health, found that once-daily TDF/FTC reduced the risk of acquiring HIV infection by 62% overall in the study population of uninfected heterosexually-active men and women. Blood level data showed that participants who became infected had far less drug in their blood, compared with matched participants who remained uninfected suggesting that medication adherence is associated with the efficacy of PrEP in preventing HIV infection.38

The Partners PrEP study (by the CDC) found that two separate antiretroviral regimens – TDF/FTC in combination and tenofovir alone – when provided to uninfected persons whose partners have HIV infection (serodiscordant couples) significantly reduced HIV acquisition (by 75% and 67%, respectively).38

A CDC study is also underway to evaluate whether PrEP is safe and effective in reducing the risk of HIV infection through injection drug use (Bangkok Tenofovir Study), but those results are not yet available.

Based on studies to date, in July 2012 the U.S. Food and Drug Administration approved the combination medication tenofovir disoproxil fumarate plus emtricitabine (TDF/FTC) for use as PrEP among sexually active adults at risk for HIV infection.38

3.3.4 Microbicides: CAPRISA and Progeny

Over the past 15 years, six microbicides have been tested in 11 clinical trials, with none showing protection. In 2010, a microbicide gel containing Gilead’s HIV drug tenofovir used by women before and after sex was shown to reduce their risk of HIV infection by nearly 40%. The Centre for the AIDS Programme of Research in South Africa (CAPRISA) trial curbed the risk of infection by the human immunodeficiency virus (HIV) by 54% among those women who used it most consistently.39 The net impact seen in the CAPRISA study reflects the combined effect of many variables, only one of them being the action of tenofovir, which penetrates into the vaginal tissue, protecting the cells that HIV targets for infection. Other variables include the prevalence of HIV infection in the male population; the number of sexual partners a woman had; the amount of AIDS virus (‘viral load’) in an infected man’s semen; concurrent use of condoms; and, most important, the consistency with which a woman used the gel. The trial was not designed to have enough statistical power to win regulatory approval for the gel. A larger trial of about 5,000 women, using the same gel but with a different dosing regimen, is under way in Africa. Results are not expected until 2013.40

Another more recent study had less substantial impacts. This study was the VOICE study – Vaginal and Oral Interventions to Control the Epidemic in sub-Saharan Africa and was
designed to evaluate the safety and effectiveness of applying vaginal gel (tenofovir gel) daily or taking tenofovir once a day. It was announced in late 2011 that the oral tenofovir and tenofovir gel arms of VOICE were dropped following interim reviews of data that determined neither product was effective in the women assigned to those study groups. See http://www.mtnstopshiv.org/node/3909.

4. What is Known of the Affordability, Feasibility, and Sustainability of the Control Strategy?

4.1 Economic Burden

The global HIV/AIDS epidemic, through its devastating scale and impact, constitutes a global emergency and undermines social and economic development throughout the world and affects all levels of society. It is no longer a health crisis but has been transformed into a development crisis. The HIV/AIDS epidemic has erased decades of progress in combating mortality and has seriously compromised the living conditions of current and future generations. It is difficult to estimate a global or even regional economic burden, given the difficulties in finding data and in aggregating disparate metrics and methods. Nonetheless, work by various authors has shown that, at the level of the firm, the cost of HIV/AIDS to businesses can be significant. For instance, a survey in 2004 in six formal sector enterprises in South Africa and Botswana provided detailed human resource, financial, and medical data. At that time, HIV prevalence in the workforces studied ranged from 7.9 to 25.0%. HIV/AIDS among employees added 0.4–5.9% to the companies’ annual salary and wage bills. The present value of an incident HIV infection ranged from 0.5 to 3.6 times the annual salary of the affected worker. Costs varied widely across firms and among job levels within firms. Key reasons for the differences included HIV prevalence, levels and stability of employee benefits, and the contractual status of unskilled workers. AIDS caused labor costs for businesses in southern Africa to rise.

4.2 Affordability

Over the past decade activist pressure, the emergence of competition from generic manufacturers, and direct negotiation with pharmaceutical companies have all contributed to a dramatic drop in the price of certain ARVs to treat HIV and AIDS in developing countries.

The availability of low cost antiretroviral drugs has been instrumental in treatment scale-up for resource-poor settings hard hit by the AIDS epidemic. Around 6.64 million people in low- and middle-income countries are currently receiving ARVs to treat HIV/AIDS. This would simply not have been possible without the reduction in the price of ARVs.

Despite significant advances, a number of problems related to the price of HIV drugs remain. Not all drugs to treat HIV and AIDS are available at a suitably low price for poor countries, meaning that many of the newer, more effective drugs are only available in the West.
Generic antiretrovirals are now widely used to treat HIV/AIDS in the developing world. They have been integrated into many treatment programmes including PEPFAR - the U.S. President's Emergency Plan for AIDS Relief. PEPFAR, the single greatest supporter of treatment provision for HIV and AIDS in the developing world, began to distribute generic drugs through its programmes in 2004-5. Generics now account for 98% of the drugs procured and supplied through PEPFAR's Supply Chain Management System (SCMS), which provides antiretroviral drugs to sixteen PEPFAR supported countries. From 2005-2008, generic ARVs allowed PEPFAR to significantly scale up its procurement of ARV drugs, without a commensurate increase in its spending on ARVs. Over this period, the increase in the proportion spent on generics by PEPFAR went from 9.2% to 76.4% and resulted in more than $300 million in cost savings.

4.3 Sustainability

For the moment, most people who need antiretrovirals in low- and middle-income countries are on first-line therapy. However, as treatment becomes more widespread, people stay on treatment for longer and resistance increases, the high price of second-line drugs is becoming a major issue. Addressing this issue will become increasingly important to ensure the most cost-effective use of available resources and the sustainability of treatment programmes. The current international financial crisis represents a major impediment to sustainable funding and the necessary increased numbers of patients on treatment.

We are already witnessing decreased funding and slow dispersal of funds across Africa, leading to decreased treatment targets and the withdrawal of care for some patients. PEPFAR has issued a system-wide recommendation to decrease scale-up and focus on sustained technical assistance. Wealthy countries are not meeting their repeatedly pledged targets, resulting in decreased support to the Global Fund and other unilateral and multilateral contributions.

5. Why Does the Disease Burden Persist?

In brief, HIV and AIDS persist in large part because there is no cure. Of course, risky behavior, governmental neglect and denial, growth of antiviral resistance and complex structural/societal factors all contribute as well. These structural factors that influence HIV transmission are deep seated within society. In the medium or long term, they can be addressed through sustained, pro-poor economic growth; poverty-reduction policies and programmes; control of injectable drug trafficking; effective judicial reforms to reduce overcrowding in prisons; improvement of employment opportunities for young adults; curtailment of human trafficking; and improvement of the public health infrastructure to support testing, counseling, tuberculosis control, and other population-based approaches to HIV/AIDS and tuberculosis. See Appendix 6.7.1.

With regard to therapeutic interventions, a safe, effective and affordable vaccine is the best hope to bring the AIDS epidemic under control. There is widespread belief among scientists that development of such a vaccine is possible. Yet, thirty years into the epidemic, the AIDS vaccine research effort faces extraordinary hurdles. See Section 6.4 below.
6. What Can Be Learned from Past/Current Research into Pharmaceutical Interventions for this Condition?

6.1 Introduction

Multiple ART drug combinations continue to successfully reduce viral load and restore immune responses in many HIV-infected individuals. However, these regimens also can result in serious toxicities and side effects, single- and multiple drug-resistance, and other complications that make them unacceptable for some individuals.

We might expect that such side effects and complications will increase as HIV-infected individuals continue to survive longer on various drug regimens and we might expect therefore more deaths occurring from liver failure, kidney disease, and cardiovascular complications in this patient population. The SMART clinical trial was one of the largest HIV/AIDS treatment trials ever conducted at that point in time. Non-AIDS related morbidity was significant in the treatment arm with CD4+ cell-guided episodic (i.e. “conserved”) treatment as there was an increase in major complications such as cardiovascular, kidney and liver diseases. These complications have been associated with ART, and it was hoped that they would be seen less frequently in those patients receiving less drug. As this does not seem to be the case with episodic/conserved therapy, and it appears that continuous antiretroviral therapy is superior to episodic therapy, it will be important to identify mortality and morbidity from all causes, not just attributed to HIV, during what appears to be the current treatment norm of continuous therapy.

Better antiretroviral drugs and treatment regimens are needed with less toxicity, increased activity in viral and cellular reservoirs, reduced ability to develop drug resistance, improved pharmacodynamics and pharmacokinetics, easier compliance, and lower cost.

The following brief summary was extracted from the BMJ Clinical Evidence series: Infection with HIV usually leads to 8–10 years of asymptomatic infection before immune function deteriorates and AIDS develops. Without treatment, about 50% of infected people will die of AIDS over 10 years. Triple antiretroviral treatments are now standard for people with HIV infection. At this point in time, the issue with respect to pharmaceutical interventions is NOT whether treatments are effective, because they are. The issue is which treatments are most effective and which new treatments need to be researched because of the development of resistance.

6.2 Antiretroviral Drug Resistance

Drug-resistant HIV-1 is a cause of growing clinical and public-health concern. As the inevitable consequence of the incomplete suppression of HIV-1 replication by antiretroviral drugs, resistance is a permanent threat for patients who are undergoing antiretroviral treatment, and transmission of resistant viruses is becoming an important concern.

Once established, resistance evolves, diversifies, and may become irreversible. Nonetheless, new drugs are becoming available that appear to retain substantial antiviral activity against HIV-1 strains that are resistant to multiple drugs. These are either drugs from existing classes
that have increased potency and improved pharmacokinetic properties or drugs from new classes that are not susceptible to cross-resistance.

Although preliminary data indicate that viral resistance to these new drugs can also develop the lessons learned about the development of viral resistance to the currently available antiretroviral drugs may prove helpful in devising treatment strategies with optimized antiviral potency that can minimize the development of resistance to these new agents.\footnote{47}

Resistance to one drug commonly confers cross-resistance to other drugs within the same therapeutic class, which suggests that sequencing strategies based on resistance should not be used. Cross-resistance is particularly common within the non-nucleoside reverse transcription inhibitor (NNRTI) class. A single mutation commonly precludes the use of all other NNRTIs.\footnote{48, 49}

The transmission of HIV drug resistance among people recently infected with HIV increased from about 1\% in 2005 to about 3\% in 2010. See Appendix 6.7.9. Among people initiating treatment in low- and middle-income countries, about 5\% had drug resistance in recent surveys, with resistance increasing somewhat with the scale-up of treatment programme coverage.

6.3 Adverse Events

With improving efficacy and patient life span, attention to adverse events (AEs) experienced with each regimen and the resulting quality of life has become a major determinant in selecting a regimen for the individual patient. Recommendations for treatment regimens are currently based on large randomized controlled trials (RCTs). These trials also serve as an important platform for assessing antiretroviral drug-related AEs. Although not all AEs appear during the limited follow-up period of RCTs, some rare AEs are revealed only after longer exposure of larger populations.\footnote{50}

Hypersensitivity to drugs in HIV-1-infected patients is about 100 times more common than in the general population.\footnote{51} A syndrome (or syndromes) of lipodystrophy affecting HIV-1-infected patients was first described only 30 years ago. The main clinical features are peripheral fat loss in the face, limbs, and buttocks and central fat accumulation within the abdomen, breasts, and over the spine. Metabolic features significantly associated with lipodystrophy include elevated blood lipids, insulin resistance and type 2 diabetes mellitus.

Table 6.7.3. lists the most common AEs from current anti-retroviral treatments, adapted from Hawkings, 2010\footnote{52} and from product labels.

Treatment for some of the most common side effects such as hypersensitivity reactions (HSR), lipodystrophy and DSPN (distal sensory polyneuropathy) remains inadequate and research must continue to find solutions. Possibly, pharmacogenomics might offer further promise of fine tuning HAART and tailoring therapy for each individual patient based on their genetic susceptibility to different ARVs.\footnote{53}
### Table 6.7.3 Adverse effects associated with different classes of antiretrovirals.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>Zidovudine</td>
<td>Anemia, nausea, rash, myopathy, dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>Stavudine didanosine</td>
<td>Nausea, lipoatrophy, DSPN, dyslipidemia, pancreatitis, lactic acidosis, hepatic steatosis, heart disease (?) DSPN</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
<td>HSR, hepatotoxicity, heart disease (?)</td>
</tr>
<tr>
<td></td>
<td>Tenofovir</td>
<td>Renal insufficiency, bone loss</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Efavirenz</td>
<td>CNS adverse effects, rash, hepatotoxicity, lipoatrophy (?), teratogenicity, hypertriglyceridemia</td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
<td>Rash, HSR, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Etravirine</td>
<td>Rash, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine</td>
<td>Depressive disorder, insomnia, headache, nausea, vomiting</td>
</tr>
<tr>
<td>&quot;QUAD&quot;</td>
<td>elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate</td>
<td>&quot;Black box&quot; warning: boxed warning for risk of potentially fatal lactic acid buildup in the blood</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td>All PIs</td>
<td>Nausea, diarrhea, rash, dyslipidemia, insulin resistance, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Atazanavir</td>
<td>Jaundice, scleral icterus, nephrolithiasis</td>
</tr>
<tr>
<td></td>
<td>Indinavir</td>
<td>Jaundice, scleral icterus, nephrolithiasis</td>
</tr>
<tr>
<td></td>
<td>Darunavir</td>
<td>Rash, poor liver function</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir</td>
<td>Diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir</td>
<td>Diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/ ritonavir</td>
<td>Diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>Tipranavir</td>
<td>Diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td>Entry inhibitors</td>
<td>Enfuvirtide</td>
<td>Injection site reactions, pneumonia, HSR</td>
</tr>
<tr>
<td>Chemokine coreceptor antagonists</td>
<td>Maraviroc</td>
<td>Cough, fever, respiratory tract infections, rash, hypotension (postural) hepatotoxicity, HSR</td>
</tr>
<tr>
<td>Integrase inhibitors</td>
<td>Raltegravir</td>
<td>Headache, insomnia, dizziness, fatigue</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir/cobicistat</td>
<td>Insomnia, abnormal dreams, rash</td>
</tr>
</tbody>
</table>

Sources: Hawkins T. 2010 Understanding and managing the adverse effects of antiretroviral therapy. *Antiviral Research* 85 (1) 201–209 / Product labels
6.4 HIV Vaccines

Is prevention of infection achievable or even feasible by the use of HIV vaccines? In general, early work suggested that scientists would not expect that a previous infection or vaccination would provide absolute protective immunity against reinfection by HIV. 54 55

Sterilizing immunity—the absence of any infection of a host cell by the agent—has rarely been seen with any vaccine. Early evidence from the poliomyelitis, measles, rubella, mumps, and influenza virus vaccine trials indicated that neither killed nor live-attenuated (nonpathogenic) viruses have prevented infection of immunized hosts by wild-type virus. 56 57 58 59 60

The AIDS vaccine development effort has already been facing various challenges. The fundamental biological challenge resides at the level of understanding the basic biology of HIV-1 infection and an effective antiviral immune response. 61

By contrast with other viruses for which there is a vaccine, the HIV infected cell can be the source of transmission and must be recognized by the immune system. Hopefully, a vaccine will stimulate the immune system sufficiently to maintain control of this virus, as is seen in the few HIV-infected individuals living for more than 20 years without symptoms and treatment. 62 In some of these patients, the virus could eventually emerge to cause disease, but only late in life when the immune system ages. Thus, in principle pathogenesis but not infection could be prevented or at least delayed a long time by vaccine.

6.4.1 The RV144 Trial

Major HIV vaccine efficacy trials conducted by VaxGen Inc (AIDSVAX 003 and AIDSVAX 004) and the NIH-supported HIV Vaccine Trials Network (HVTN 502 and HVTN 503) failed to demonstrate efficacy. However, a recent trial conducted in Thailand (RV144 trial) demonstrated a low level of efficacy, resulting in some renewed optimism. 63

The vaccine regimen tested in Thailand consisted of priming with a genetically engineered viral vector carrying three synthetic HIV genes. The priming was followed by booster inoculations with two recombinant envelope proteins from HIV, clade B and E. The results showed no efficacy in a Phase III trial in Thai injecting drug users. Although the trial had been criticized scientifically, RV144 showed that, by modified intent-to-treat analysis, 3.5 years after initial vaccination, the vaccine regimen was 31.2 % efficacious in preventing HIV infection. There was no effect on early post-infection HIV-1 RNA viral load or CD4+ T-cell count. 46

This is very modest efficacy but it is the first evidence that a safe and effective preventive HIV vaccine is possible. In September 2011, additional follow-up analysis of the RV144 Thai vaccine trial revealed a significant discovery. Aiming to better understand how RV144 protected against HIV infection, the study team found two important molecular clues—two antibodies correlated with the risk of HIV infections. The highly-anticipated post hoc analysis of RV144 and an array of new insights into the mechanics of broadly neutralizing antibodies against HIV have brought the vaccine field closer than ever before to finding a strategy for an effective HIV vaccine. 64
Additionally, the Pox-Protein Public Private Partnership (P5) is working to develop a regimen that will be tested in follow-on trials to RV144. See Appendix 6.7.11.

6.4.2 Selected Obstacles to HIV-Vaccine Development and Their Implications

Current AIDS vaccine candidates are unable to induce broadly neutralizing antibodies (bNAb) against primary HIV isolates or only to a very limited and narrow extent, presenting a major stumbling block in the development of an effective HIV vaccine. The immune response elicited by a successful vaccine possibly will require both antibodies and T cells that recognize, neutralize and/or inactivate diverse strains of HIV and that reach the site of infection before the infection becomes irreversibly established.

- Extensive viral subtype and sequence diversity limits the efficacy of current vaccine approaches to specific subtypes.
- There is a narrow window of opportunity for the immune system to clear initial infection before early establishment of latent viral reservoirs.
- The immune correlates of protection remain unknown.
- Viral escape from humoral and cellular immune responses may limit sustained efficacy.
- Conserved antibody targets on the outer envelope protein are hidden.
- There is a lack of a predictive animal model.
- Still limited interest of the pharmaceutical industry.

7. What is the Current “Pipeline” of Products that Are to Be Used for this Particular Condition?

Tracking pharmaceutical pipelines over time reveals various therapeutic candidates appearing and disappearing, only to be replaced by other hoped-for products. Thus, snapshots of HIV pipelines need to be viewed as a ‘work in progress’. Table 6.7.4 is adapted from information provided by the Pharmaceutical Manufacturers of America, but it is not intended to be a fully comprehensive view of the United States pipeline. We attempted to place each intervention into its appropriate therapeutic class (e.g. protease inhibitor, NNRTI, and so on) although this is not always possible.
Table 6.7.4: The current development pipeline of HIV medicines in US

<table>
<thead>
<tr>
<th>Integration</th>
<th>Transcription</th>
<th>Virus Assembly</th>
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<tbody>
<tr>
<td>Elvitegravir</td>
<td>ALX40-4C</td>
<td>bevirimat</td>
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<td>GSK1349572</td>
<td>CGP64222</td>
<td>vivecon</td>
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<tr>
<td>MK-2048</td>
<td>L50</td>
<td></td>
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<tr>
<td></td>
<td>RNAi</td>
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<td></td>
<td>DRB</td>
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</table>

<table>
<thead>
<tr>
<th>CD4 binding</th>
<th>CCR5 binding</th>
<th>Fusion</th>
<th>Reverse transcription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-542</td>
<td>PSC-RANTES</td>
<td>T-1249</td>
<td>NRTI</td>
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<td>AOP-RANTES</td>
<td>5-helix</td>
<td>atevirdine</td>
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<td>TNX-355</td>
<td>NNY-RANTES</td>
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<td>amdoxovir</td>
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<td>TAK-779</td>
<td></td>
<td>apricitabine</td>
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<tr>
<td></td>
<td>vicriviroc</td>
<td></td>
<td>celevudine</td>
</tr>
<tr>
<td></td>
<td>aplaviroc</td>
<td></td>
<td>elvucitabine</td>
</tr>
<tr>
<td></td>
<td>Pro-140</td>
<td></td>
<td>entecavir</td>
</tr>
</tbody>
</table>


We analyzed the United States clinical trials database ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) to develop another estimate of the pipeline activity—the clinical trial sponsoring organizations.

Figure 6.7.3 (See Annex 6.7.2) summarizes the information as of the original Report (late 2003) and as of late 2012 shown as side-by-side comparisons on the bar graph (2003 data on the left/2012 data immediately adjacent). The number in parenthesis on the X-axis is the proportion of total HIV interventional clinical trials in the database on that date relegated to that sponsor. ¹

The greatest total number of clinical trials related to HIV (primarily early stage Phase I and Phase II trials) is being sponsored by the National Institutes of Health. Significantly, the fraction of total HIV trials conducted by the NIH has decreased from 54% to 37%, since the original Report as the difference is being taken up by universities and non-governmental organizations. The proportion of total HIV trials sponsored by the industry has changed little since 2003, although the total numbers of trials have increased across the board since 2003.

¹ The search term “HIV” included HIV therapeutics, vaccines HIV diagnostics, drug to drug comparisons, opportunistic infections, side effects (cardiac effects, lipodystrophy and the like).
Figure 6.7.3: Total Number of HIV related clinical trials (as of October 2003 and November 2012)

As for HIV vaccine trials, as of 16 Nov 2012, the results are presented below in Table 6.7.5.

Table 6.7.5: HIV vaccine trials

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>190</td>
<td>104</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Other Federal Government</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>All industry</td>
<td>85</td>
<td>49</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>University/Other Organizations</td>
<td>53</td>
<td>35</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>

Source: United States clinical trials database (www.clinicaltrials.gov)
There appears to be far less information about European HIV clinical trials that is available. We searched the same www.clinicaltrials.gov database but restricted the search to the UK, France and Germany for all interventional HIV trials. As of 16 November 2012, there are 437 European (UK + France + Germany) studies allocated as follows: 84 Phase I, 149 Phase II, 150 Phase III and 67 Phase IV.

8. What is the Current Status of Institutions and Human Resources Available to Address the Disease?

8.1 Introduction

Given the number of institutions and human resources involved in the HIV pipeline, we can state with some confidence that the private research and development (R&D) sector in the United States and Europe is already heavily investing in addressing this disease. The United States has by far the greatest financial and human resource contribution in this regard (see Section 7). We note, however, that there appears to be no paucity of private funding with regard to HIV R&D, the clinical trial analysis shows the United States government (NIH) supporting the majority of clinical trials.

8.2 Public Funding for HIV/AIDS in the European Union

Overall, from 2007 to 2010, the EU invested an average of nearly €250 million a year in R&D to develop new tools to prevent, diagnose and treat HIV & AIDS, TB and malaria. See Appendix 6.7.12. About €80 million a year was directed to HIV/AIDS during this time and this number is dominated by the United States investment in R&D for HIV/AIDS.

8.2.1 Framework 7

Research on HIV/AIDS is a top priority for the European Commission. Projects financed under Framework Programme 6 (FP6) are progressing through the development of new vaccines, microbicides, drugs and therapeutic options. Two “networks of excellence” have been created, one for HIV prevention, and the other one for HIV treatment, with the participation of most of the top European HIV researchers and clinicians. Moreover, in order to allow further development of successful products, the European and Developing Countries Clinical Trials Partnership (EDCTP; http://www.edctp.org/), has the ability to finance capacity building and clinical trials in sub-Saharan Africa.

In FP7, the first four proposal calls (2007-2010) were for €83 million, yielding over 15 projects. HIV/AIDS prevention funding over this time period was about €43.5 million directed to new HIV vaccines inducing broadly-reactive neutralizing antibodies, discovery and/or development of new and promising anti-HIV microbicides, transcutaneous and mucosal HIV vaccine based on novel delivery strategy (See below: CUT’HIVAC). An additional € 34.5 million was allocated for therapeutics, paediatric formulations of ARVs. http://ec.europa.eu/health/sti_prevention/docs/ev_20100505_co04_en.pdf
Within the area of HIV FP7 has funded one very large project to foster utilization of clinical care data to improve pharmacotherapy: EuroCoord – Coordinating the A-Z of HIV. It is expected that funding this or similar initiatives will continue in Horizon 2020. See http://www.eurocoord.net/.

Examples of other FP7 projects extending over the next several years are the following:

- **HIVERA**: Harmonizing, Integrating and Vitalizing European Research on HIV/AIDS (2010-2014). This is a coordination/networking activity (Total cost: €2 434 320. EU contribution: €2 million) proposed as a dedicated ERA-NET paving the way for the coordination and cooperation of national programmes, starting first in 8 countries (BE, DE, EE, FR, IT, PT, RO, TR), but flexible enough to integrate new Member States by the end of the Grant duration. Duplicating existing European activities will be avoided by actively linking up HIVERA with ongoing existing networks and the EDCTP, and by concentrating pilot joint calls on emerging issues in HIV/AIDS.

- **COBRA**: Co-morbidity in relation to Aids (2013-2017). This is a focused research project (Total cost: €7 800 378. EU contribution: €5 998 758) designed to understand age-associated comorbidities (diabetes, cardiovascular conditions, osteoporosis) that occur in persons on long-term ARVs, the object of which is to conduct longitudinal HIV cohort studies in Amsterdam and London to find a robust estimate of the effect of treated HIV infection on the prevalence, incidence and age of onset of these co-morbidities.

- **PREVENTIT**: Point-of-Care Device for Syphilis and HIV in Pregnant Women and New Born (2012). This is a focused research project (Total cost: €2 870 242. EU contribution: €2 097 373) designed to develop, validate and start manufacturing of a multi-analyte device for the diagnosis of congenital syphilis and HIV co-infections.

- **HIVBIOCHIP**: Point-of-care Biochip for HIV Monitoring in the Developing World (2012-2017). This is a starting grant (Total cost: €1 986 000. EU contribution: €1 986 000) to develop a portable, inexpensive imaging system for counting the absolute number of CD4 cells from whole blood.

Diagnostics are also being tested.

- **PREVENTIT**: Point-of-Care Device for Syphilis and HIV in Pregnant Women and New Born (2012). This is a focused research project (Total cost: €2 870 242. EU contribution: €2 097 373) designed to develop, validate and start manufacturing of a multi-analyte device for the diagnosis of congenital syphilis and HIV co-infections.

Biomarkers are not being tested at the moment but they might be important to judge the efficacy of vaccines. Adherence is currently not a priority area within HIV. There are only some projects around adherence that are supported involving mHealth. They are funded by the public health program of FP7. There is relatively little research on development of diagnostics. Several of the projects are on capacity building in research and clinical care. (Personal communication, Dr. Alessandra Martini, European Commission Directorate-General for Research and Innovation Scientific Officer, Infectious Diseases)

Vaccines are a priority, albeit in combination with other interventions. There are currently some candidates which are promising and are currently tested in phase I clinical trials (CUTHIVAC is one important example of a study that is funded by FP7 on vaccine development http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_LANG=EN&PJ_RC N=11121837&pid=0&q=7B76A86D11A45DCA1AE16FD9356572C2&type=adv).
FP7: CUT’HIVAC: Cutaneous and mucosal HIV vaccination: 2010 to 2014

This is a large-scale integrated project with 15 partners. Clinical trials will be implemented with combined vaccination by transcutaneous, intradermal routes and/or mucosal administration of HIV-envelop protein-based vaccine. The total cost is over €15 million and the EU contributes nearly €12 million. See http://cordis.europa.eu/projects/index.cfm?fuseaction=app.details&TXT=HIV&FRM=1&STP=10&SIIC=&PGA=&CCY=&PCY=&SRC=&LN=G=en&REF=93671

8.3 Public Funding for HIV/AIDS in the United States

President Obama’s Fiscal Year (FY) 2013 federal budget request (including NIH and many other HIV related activities, not all R&D), released on February 13, 2012, includes an estimated Domestic HIV/AIDS funding at US$ 22.25 billion. The FY 2013 request represents a 3% increase (US$ 766 million) over FY 2012 levels.

Federal funding for HIV/AIDS, however, represents a small fraction (<1%) of the overall federal budget of the United States. The FY 2013 budget request for HIV/AIDS includes US$ 6.2 billion for the global epidemic, 3% less than FY 2012. Of this amount, US$ 4.5 billion is for the following: bilateral activities centrally operated at the Office of the Global AIDS Coordinator and in countries and regions (approximately US$ 4.1 billion); international research (US$ 389 million); and multilateral contributions to UNAIDS (US$ 45 million), the International AIDS Vaccine Initiative (US$ 28.7 million), and Microbicides (US$ 45 million). The request also includes US$ 1.65 billion for the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), a 27% increase over FY 2012 funding levels. See http://kaiserfamilyfoundation.files.wordpress.com/2013/01/7029-08.pdf.

8.4 Private Sector R&D Funding

8.3.1 Product Development Partnerships for HIV

Product Development Partnerships (PDPs) are playing an increasingly important role in the development of new medicines for neglected diseases of the developing world.²⁹

The International AIDS Vaccine Initiative (IAVI) in 2007 provided US$ 81 297 482 for HIV/AIDS vaccine development. The International Partnership for Microbicides (IPM) provided US$ 46 311 916, the Program for Appropriate Technology in Health (PATH) provided US$ 745 000 (out of a total funding stream of US$ 38 024 679) for various “unspecified” HIV projects, and the World Health Organization: Special Programme for Research and Training in Tropical Diseases (WHO/TDR) provided US$ 3 228 410 (out of a total of US$ 32 675 307) for HIV/AIDS diagnostics.³² See also Appendix 6.7.11.

8.4 Paediatric fixed dose combinations

In July 2012, the Drugs for Neglected Diseases Initiative (DNDi), a not-for-profit research and development (R&D) organization, announced a new collaboration with Indian drug manufacturer Cipla to develop and produce an improved first-line antiretroviral (ARV) combination therapy specifically adapted to meet the treatment needs of infants and toddlers living with HIV/AIDS.²⁰
Fixed-dose combination dissolvable ‘baby pills’ (for example Triomune® Baby and Junior produced by Cipla in 2007) are used throughout most of Africa, but they are not optimal for the youngest children who have very high levels of virus in their blood and have already been exposed to some of these drugs from their mother. An important alternative drug (Kaletra®: lopinavir-ritonavir protease inhibitor) has been used mainly in South Africa, but has problems, including poor taste, impractical multiple liquid preparations that are cumbersome to transport, requirements for refrigeration, high cost, difficulties for caregivers to administer, and negative interactions with tuberculosis (TB) drugs. The goal of the collaboration between DNDi and Cipla is to develop a 4-in-1 ARV combination product for HIV-infected children under the age of three years, including those who have been exposed to drugs while in the womb, and also those who are coinfected with TB.

Historically, major pharmaceutical companies have invested little in R&D specifically aimed at addressing the needs of young children with HIV/AIDS largely because of the absence of a viable market. This is because the virtual elimination of mother-to-child transmission of HIV in high-income countries means that nearly all HIV-positive children live in low- and middle-income countries, with over 90% in sub-Saharan Africa.

Cipla will work with DNDi and other partners to test new combinations of HIV treatment for infants and young children, such as a fixed-dose combination of lopinavir/ritonavir (LPV/r) 40-/10-mg sprinkle formulation (‘Lopimune Sprinkles’), combined with one of two other powerful ARV drug combinations, abacavir/lamivudine (ABC/3TC) or zidovudine/ lamivudine (AZT/3TC). Cipla will work to produce an appropriate 4-in-1 combination sachet product, in which the four ARV drugs will be in taste-masked, granular form, for easy mixing into food or liquids such as water, juice, or breast milk, with the aim of registering the drug by 2015.

In early December 2012, UNITAID in Geneva committed up to US$ 120 million for specific projects, among them a grant of up to US$ 17.3 million to DNDi to make child-adapted paediatric HIV treatments available. In addition to these principle grants, the UNITAID Executive Board approved four “market entry” grants to help manufacturers of “point-of-care” HIV diagnostic machines in the final stages of development. UNITAID also provided up to US$ 8 million to continue a project which ensures that procurement of paediatric HIV medicines will continue into 2013 and 2014.

8.5 HIV Vaccine R&D

Since 2001, global preventive HIV vaccine R&D investment has an average yearly investment of US$ 824 million (a major portion of which is provided by the entities shown in the Figures above). The 2011 total investment represents an overall 12% drop since the height of vaccine funding in 2007. See Appendix 6.7.13 at: http://www.hivresourcetracking.org/sites/default/files/HIV%20Vaccine%202011%20Funding%201-pager.pdf.

United States government agencies alone accounted for 74% (US$ 623 million) of all HIV vaccine R&D funding, again reflected as the National Institutes of Health (NIH) in Figure 6.7.5, below. Investment by European governments was US$ 48.5 million in 2011, a decrease of over US$ 12 million (21%) from the previous year and a 40% decrease from their US$ 82 million peak in 2006. Philanthropic investments in HIV vaccine R&D increased in 2011 by US$ 10 million (10%), as new philanthropic groups entered the funding space and as others,
such as the United Kingdom’s (UK) Wellcome Trust and the Spanish Fundació la Caixa, increased their funding. See Appendix 6.7.13.

The year 2011 saw lower United States public-sector investment in HIV vaccines and the end of the United States stimulus funding to the NIH, along with decreased European investment overall. Yet, philanthropic investment increased in 2011, offsetting cuts to public-sector funding. Investment overall decreased by 2%, an effective flat lining of funding. In an age of economic challenges, continued investment without significant cuts can be considered a sign that the top funders understand the importance of continuing to invest in HIV prevention R&D, but this sustained funding will need to be supplemented as new strategies are explored and promising candidates move toward more expensive late-stage vaccine trials. See Appendix 6.7.13.

### 8.6 Overall HIV Funding: Response of donors/governmental funders to the HIV epidemic post 2003

In 2003, the United States government announced the United States President’s Emergency Plan for AIDS Relief (PEPFAR). At US$ 15 billion over five years, it was the largest single funding commitment for a disease in history. PEPFAR was reauthorized in 2008 for up to US$ 48 billion to combat AIDS, TB and malaria from 2009 to 2013. Additional innovations in global health funding followed. By 2006, Brazil, Chile, France, Norway and the United Kingdom had agreed to create UNITAID, an international drug purchase facility financed through a modest levy on airline tickets.

Due probably to the global economic situation, in recent years domestic and international HIV-specific funding has decreased from US$ 15.9 billion in 2009 to US$ 15 billion in 2010. International assistance declined from US$ 8.7 billion in 2009 to US$ 7.6 billion in 2010.71

However, global spending on HIV has increased, totaled about US$ 16.8 billion in 2011, up from the 2010 estimate. See Appendix 6.7.1. Domestic public spending continues to increase, with some low- and middle-income countries now funding their own response, however, HIV programmes in low-income countries still rely on external aid to a much greater extent than the health sector overall.

#### 8.6.1 Medicines and basic research for LMIC research: Top 12 Funders (G-Finder)


For basic research, this was defined as research into mechanisms related to preventative vaccines and microbicides (e.g. immunological responses to potential antigens, mechanisms of mucosal transmission) but excluding general research that could also be applied to commercial products.

Research into HIV drugs also included only developing-country-specific applications, such as label extensions to paediatric patient groups, fixed dose combinations, and slow release formulations. These restrictions were important to prevent developing-country-specific
funding being swamped by the high level of public and private investment into HIV R&D targeted at Western needs.

Overall, as in previous years, the three ‘top tier’ diseases – HIV/AIDS, malaria and tuberculosis (TB) – again received approximately one-third to one-fifth of total global neglected disease R&D funding each, with HIV/AIDS receiving about one-third of the total for 2011. Nonetheless, this share continued to decline, with cuts for HIV/AIDS (down US$ 41.1m (-4.0%) from 2010 to about US$ 1 billion).

As defined, this HIV/AIDS R&D funding was highly concentrated with 12 groups providing 93.6% of funding. See Figure 6.7.4 and 6.7.5 extracted from the G-FINDER database (See Annex 6.7.3). Decreases in HIV funding in 2011 were widespread, with ten of the top 12 funders reducing funding from 2010. Although the U.S. National Institutes of Health remained by far the largest funder, contributing 61.4% (US$ 631.4 million) of the global total, it also registered the biggest drop in funding in 2011 (down US$ 26 million, -3.9%). Of the top 12 funders, only the U.S. Department of Defense (DOD) and the Wellcome Trust increased funding.

In 2011, the public and philanthropic sectors collectively provided 97.8% of HIV/AIDS R&D funding, with the public sector providing 84.6% (US$ 870.5 million) of total funding and the philanthropic sector providing 13.1% (US$ 135.2 million). Public funding accounts for the majority of HIV/AIDS R&D funding, therefore public sector budget cuts following the global financial crisis have had a large impact.
Figure 6.7.4: Top 12 HIV/AIDS R&D Funders (% of the top 12 annual funding)


Note: Figures are adjusted for inflation and reported as 2007 US dollars
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Figure 6.7.5: Top 12 HIV/AIDS R&D Funders (Value of top 12 annual funding)

Note: Figures are adjusted for inflation and reported as 2007 US dollars

9. Ways Forward from a Public Health Viewpoint with Regard to Public Funding

9.1 Gaps Between Current Research and Potential Research Issues which Could Make a Difference

There are some problems with current HIV therapeutics. Among these are emergence of drug resistant HIV variants, adverse effects, metabolic abnormalities and toxicities, poor adherence to complex, multi-drug regimens, and primary infection with drug-resistant and multi-resistant HIV variants. Thus, notwithstanding the large pipeline and private sector investments, therapeutics discovery and development remains a critical activity:
Update on 2004 Background Paper, BP 6.7 HIV/AIDS

- new delivery or formulation methods to enhance the clinical potential of anti-HIV drugs (FDA-approved or those undergoing clinical testing) in infected adults and children;
- validating new viral and cellular targets for HIV inhibition and for developing new drugs (or developing new agents against existing targets).
- Continued development of HIV vaccines and microbicides

9.2 What is the Comparative Advantage of the EU with Regard to Public Funding of Pharmaceutical R&D?

The European Union cannot match the private or public funding levels of the United States with regard to HIV research and development (See Figures 6.7.4 and 6.7.5). However, based upon what we understand to be the epidemiology of HIV/AIDS in expanded Europe and the rest of the world, and the current states of private and public sector institutions in this regard, we believe the European Union can, from a public health viewpoint, fill gaps in the following areas:
- Target affected populations, especially women, injecting drug users (IDUs), children, adolescents, older adults, and across racial/ethnic groups. Conduct studies that permit evaluation of potential differences in response to therapy due to gender and/or racial or ethnic differences. We believe the opportunities clearly exist to conduct clinical studies into specialized populations in Africa, possibly with EDCTP involvement.
- Promote innovative mechanisms of funding to attract additional investigators to undertake multidisciplinary research on microbicides discovery and development.
- Expand capacity (infrastructure and human resources) and strengthen coordination to conduct Phase II/III microbicides and fixed dose combination clinical trials.

10. Conclusion

Globally the number of people newly infected with HIV is decreasing. First-line treatments are effective and fairly inexpensive, second line treatments are effective but expensive. At this point, access to treatment and prevention efforts must continue. We are not yet close to an effective vaccine.

In Eastern Europe the number of infected people continues to rise. The annual incidence (rate of newly diagnosed HIV cases) was stable in central and western Europe between 2004 and 2009, whereas it increased by two-thirds in eastern Europe and Central Asia. In the European region, the HIV epidemic continues to spread and treatment is not keeping pace with new infections.

There is sufficient scientific evidence, as well as an extensive pool of normative guidance, on all aspects of HIV prevention, treatment and care. Aligning national legislation and policies with internationally recognized standards and ensuring their effective implementation will contribute to a successful response to the HIV epidemic.
References


11. United States Department of Health and Human Services, NIH Discal Year 2005 Budget Request Jack Whitescarver, Ph.D. Director, Office of AIDS Research April 1, 2004


13. ECDC / European Monitoring Centre for Drugs and Addiction (2011)


40 Centre for the AIDS Programme of Research in South Africa, CAPRISA at http://www.caprisa.org/SitePages/Home.aspx


43 PEPFAR(2011, April) Statement of Ambassador Eric Goosby, MD, US Global AIDS Coordinator, US Department of State, Before the US Senate Committee on Foreign Relations, Subcommittee on African Affairs


Figure 6.7.6: HIV-1 life cycle and potential opportunities for therapeutic intervention

Annexes

Annex 6.7.1: Standardized death rates (per 100,000 people) for HIV/AIDS among country-components of the European Union

<table>
<thead>
<tr>
<th>Year</th>
<th>EU</th>
<th>0000 SDR, All causes, per 100000</th>
<th>0060 SDR, Infectious and parasitic diseases, per 100000</th>
<th>% infec/parasitic of all causes</th>
<th>0120 SDR, Intestinal infectious diseases, per 100000</th>
<th>0180 SDR, Tuberculosis, per 100000</th>
<th>0300 SDR, AIDS/HIV (as recorded by routine mortality statistics system), per 100000</th>
<th>% AIDS/HIV of infectious/parasitic</th>
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</thead>
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<tr>
<td>1995</td>
<td>EU</td>
<td>811.75</td>
<td>6.82</td>
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<td>2.02</td>
<td>3.7</td>
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<td>EU</td>
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<td>8.11</td>
<td>1.13%</td>
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<td>1.57</td>
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<td>0.92</td>
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<td>8.6</td>
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### Update on 2004 Background Paper, BP 6.7 HIV/AIDS

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<td>1997</td>
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<td>690.91</td>
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<td>0.39</td>
<td>0.93</td>
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<td>0.68</td>
<td>0.57</td>
<td>1.35</td>
<td>1.985294118</td>
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<td>0.57</td>
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<td>1.05</td>
<td>0.52</td>
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<td>2008</td>
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<td>555.77</td>
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<td>1.16</td>
<td>0.44</td>
<td>1.05</td>
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<tr>
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<td>1.03</td>
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## Update on 2004 Background Paper, BP 6.7 HIV/AIDS

<table>
<thead>
<tr>
<th>Year</th>
<th>EU members since 2004 or 2007</th>
<th>0000 SDR, All causes, per 100000</th>
<th>0060 SDR, Infectious and parasitic diseases, per 100000</th>
<th>% infec/parasitic of all causes</th>
<th>0120 SDR, Infectious diseases, per 100000</th>
<th>0180 SDR, Tuberculosis, per 100000</th>
<th>0300 SDR, AIDS/HIV (as recorded by routine mortality statistics system), per 100000</th>
<th>% AIDS/HIV of infectious/parasitic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>EU members since 2004 or 2007</td>
<td>1124.94</td>
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<tr>
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<td>5.55</td>
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<td>5.55</td>
<td>0.67</td>
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<td>0.43</td>
<td>5.22</td>
<td>0.75</td>
<td>1.744186047</td>
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<td>0.38</td>
<td>4.78</td>
<td>0.6</td>
<td>1.578947368</td>
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<tr>
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<td>8.17</td>
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<td>0.41</td>
<td>4.59</td>
<td>0.59</td>
<td>1.43902439</td>
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<tr>
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<td>988.19</td>
<td>8.21</td>
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<td>0.31</td>
<td>4.65</td>
<td>0.59</td>
<td>1.903225806</td>
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<td>0.37</td>
<td>4.32</td>
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<td>0.3</td>
<td>4.19</td>
<td>0.41</td>
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<tr>
<td>2004</td>
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<td>950.26</td>
<td>7.18</td>
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<td>0.41</td>
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<td>0.75%</td>
<td>0.23</td>
<td>3.49</td>
<td>0.4</td>
<td>1.739130435</td>
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<td>2006</td>
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<td>6.93</td>
<td>0.76%</td>
<td>0.23</td>
<td>3.29</td>
<td>0.38</td>
<td>1.652173913</td>
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<tr>
<td>2007</td>
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<td>899.33</td>
<td>6.88</td>
<td>0.77%</td>
<td>0.21</td>
<td>3.15</td>
<td>0.39</td>
<td>1.857142857</td>
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<td>2008</td>
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<td>874.12</td>
<td>7.33</td>
<td>0.84%</td>
<td>0.23</td>
<td>3.09</td>
<td>0.41</td>
<td>1.782608696</td>
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<td>0.28</td>
<td>2.78</td>
<td>0.35</td>
<td>1.25</td>
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<tr>
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<td>0.85%</td>
<td>0.35</td>
<td>2.5</td>
<td>0.39</td>
<td>1.114285714</td>
</tr>
</tbody>
</table>

EU: the 27 Member States of the European Union;
·EU members before May 2004: the 15 Member States of the European Union prior to 1 May 2004;
·EU members since 2004 or 2007: the 12 new Member States of the European Union from 1 May 2004 or 1 January 2007;
Annex 6.7.2: Number of Clinical Trials, including those no longer recruiting

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
<th>Totals</th>
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<tbody>
<tr>
<td>2003 NIH (54%)</td>
<td>343</td>
<td>288</td>
<td>130</td>
<td>26</td>
<td>788</td>
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<tr>
<td>2012 NIH (37%)</td>
<td>566</td>
<td>604</td>
<td>221</td>
<td>67</td>
<td>1458</td>
</tr>
<tr>
<td>2003 Other Federal Government (.76%)</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>2012 Other Federal Government (2%)</td>
<td>20</td>
<td>37</td>
<td>26</td>
<td>15</td>
<td>98</td>
</tr>
<tr>
<td>2003 All industry (40%)</td>
<td>200</td>
<td>226</td>
<td>133</td>
<td>29</td>
<td>588</td>
</tr>
<tr>
<td>2012 All industry (39%)</td>
<td>466</td>
<td>505</td>
<td>356</td>
<td>223</td>
<td>1550</td>
</tr>
<tr>
<td>2003 University/Other Organizations (4.7%)</td>
<td>23</td>
<td>23</td>
<td>15</td>
<td>7</td>
<td>68</td>
</tr>
<tr>
<td>2012 University/Other Organizations (21%)</td>
<td>219</td>
<td>261</td>
<td>160</td>
<td>190</td>
<td>830</td>
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</table>

Note: Searched under sponsor "HIV infections." There are some overlaps (unknown) in sponsor
Annex 6.7.3: Top 12 HIV/AIDS R&D funders for Low and Middle Income Countries

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2007 % of TOTAL IN 2007</th>
<th>2008</th>
<th>2008 % of TOTAL IN 2008</th>
<th>2009</th>
<th>2009 % of TOTAL IN 2009</th>
<th>2010</th>
<th>2010 % of TOTAL IN 2010</th>
<th>2011</th>
<th>2011 % of TOTAL IN 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US NIH</strong></td>
<td>678 816 000</td>
<td>62.68%</td>
<td>643 838 823</td>
<td>55.27%</td>
<td>688 900 175</td>
<td>60.51%</td>
<td>657 340 665</td>
<td>61.26%</td>
<td>631 394 882</td>
<td>61.38%</td>
</tr>
<tr>
<td><strong>Gates Foundation</strong></td>
<td>91 975 642</td>
<td>8.49%</td>
<td>160 531 263</td>
<td>13.78%</td>
<td>119 431 387</td>
<td>10.49%</td>
<td>118 655 020</td>
<td>11.06%</td>
<td>110 940 741</td>
<td>10.78%</td>
</tr>
<tr>
<td><strong>USAID</strong></td>
<td>67 457 000</td>
<td>6.23%</td>
<td>67 813 102</td>
<td>5.82%</td>
<td>68 169 518</td>
<td>5.99%</td>
<td>68 385 015</td>
<td>6.37%</td>
<td>65 005 117</td>
<td>6.32%</td>
</tr>
<tr>
<td><strong>US DOD</strong></td>
<td>27 800 000</td>
<td>2.57%</td>
<td>24 448 940</td>
<td>2.10%</td>
<td>34 236 010</td>
<td>3.01%</td>
<td>31 671 138</td>
<td>2.95%</td>
<td>42 188 575</td>
<td>4.10%</td>
</tr>
<tr>
<td><strong>Aggregate industry</strong></td>
<td>19 635 626</td>
<td>1.81%</td>
<td>47 449 865</td>
<td>4.07%</td>
<td>35 342 218</td>
<td>3.10%</td>
<td>30 103 341</td>
<td>2.81%</td>
<td>22 969 327</td>
<td>2.23%</td>
</tr>
<tr>
<td><strong>UK MRC</strong></td>
<td>31 151 182</td>
<td>2.88%</td>
<td>28 718 490</td>
<td>2.47%</td>
<td>38 305 345</td>
<td>3.36%</td>
<td>21 050 427</td>
<td>1.96%</td>
<td>16 638 498</td>
<td>1.62%</td>
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<tr>
<td><strong>European Commission</strong></td>
<td>24 794 890</td>
<td>2.29%</td>
<td>26 305 301</td>
<td>2.26%</td>
<td>27 100 813</td>
<td>2.38%</td>
<td>19 073 421</td>
<td>1.78%</td>
<td>18 564 822</td>
<td>1.80%</td>
</tr>
<tr>
<td><strong>Russian MHSD</strong></td>
<td>16 666 666</td>
<td>1.54%</td>
<td>16 055 877</td>
<td>1.38%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>French ANRS</strong></td>
<td>10 511 570</td>
<td>0.97%</td>
<td>14 700 289</td>
<td>1.26%</td>
<td>11 919 251</td>
<td>1.05%</td>
<td>11 141 961</td>
<td>1.04%</td>
<td>9 490 184</td>
<td>0.92%</td>
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<tr>
<td><strong>UK MRC</strong></td>
<td>13 101 548</td>
<td>1.21%</td>
<td>11 635 919</td>
<td>1.00%</td>
<td>11 737 927</td>
<td>1.03%</td>
<td>11 940 880</td>
<td>1.11%</td>
<td>6 767 982</td>
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<tr>
<td><strong>Wellcome Trust</strong></td>
<td>6 932 786</td>
<td>0.64%</td>
<td>9 429 787</td>
<td>0.81%</td>
<td>9 296 776</td>
<td>0.82%</td>
<td>11 423 726</td>
<td>1.06%</td>
<td>16 813 469</td>
<td>1.63%</td>
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<tr>
<td><strong>Inserm</strong></td>
<td>342 620</td>
<td>0.03%</td>
<td>1 180 483</td>
<td>0.10%</td>
<td>12 497 386</td>
<td>1.10%</td>
<td>13 931 413</td>
<td>1.30%</td>
<td>13 841 576</td>
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</tr>
<tr>
<td><strong>Disease Total</strong></td>
<td>1 083 018 193</td>
<td>1.00%</td>
<td>1 164 882 551</td>
<td>1.00%</td>
<td>1 138 511 159</td>
<td>1.00%</td>
<td>1 073 033 520</td>
<td>1.00%</td>
<td>1 028 723 121</td>
<td>1.00%</td>
</tr>
</tbody>
</table>
Appendices

Appendix 6.7.1 Together we will end AIDS, (2012). UNAIDS
Appendix 6.7.7 2011 Annual report on the state of the drugs problem in Europe. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)
Appendix 6.7.8 Joint EMCDDA and ECDC rapid risk assessment; HIV in injecting drug users in the EU/EEA, following a reported increase of cases in Greece and Romania, (2012). The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)
Appendix 6.7.13 Funding for HIV Vaccine R&D in 2011. HIV Vaccines and Microbicides Resource Tracking Working Group