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AN OVERVIEW OF HIV TREATMENTS: WHAT TO START

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Abstract: Combinations of HAART using 2 NRTIs plus NNRTIs or PIs (zidovudine, abacavir or tenofovir plus lamivudine, or emtricitabine plus tenofovir) are preferred treatment of HIV infection internationally and in Australia.Some antiretroviral should not be combined due to overlapping toxicities and potential viral antagonism (e.g. Atazanavir + indinavir, didanosine + stavudine). The challenges for treating HIV infection will be to reduce adverse effects, drug resistance, and increased options for treatment-experienced patients (HIV patient with previously treated using ARV).

Human immunodeficiency virus (HIV) a retrovirus that causes *acquired immunodeficiency syndrome* (AIDS), a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections. HIV is an epidemic disease that continues to be a significant public health issue around the world.

Infection with HIV is associated with a progressive decrease of the $CD4^+$ T cell count and an increase in viral load. Unaids report, almost 36.1 million people are infected HIV in the world in the end of 2000, and by the end of 2010, Unaids predict it will increase twice more. The use of highly active antiretroviral therapy (HAART) combination for treating HIV infection has transformed HIV infection from a death sentence into a chronic manageable disease, which is essential for the treatment of HIV.

In Australia and developing countries, the choice of combination regimens for treatment-experience patients is more complex. Some antiretrovirals should not be combined due to overlapping toxicities and potential viral antagonism.

This review identifies effective combinations of HAART that are likely to become ideal treatment of HIV infection internationally and in Australia by 2010.

Region	Adults & children living with HIV/AIDS	Adults & children newly infected	Adult prevalence*	Deaths of adults & children
Sub-Saharan Africa	22.4 million	1.9 million	5.2%	1.4 million
North Africa & Middle East	310,000	35,000	0.2%	20,000
South and South-East Asia	3.8 million	280,000	0.3%	270,000
East Asia	850,000	75,000	<0.1%	59,000
Oceania	59,000	3900	0.3%	2,000
Latin America	2.0 million	170,000	0.6%	77,000
Caribbean	240,000	20,000	1.0%	12,000
Eastern Europe & Central Asia	1.5 million	110,000	0.7%	87,000
North America	1.4 million	55,000	0.4%	25,000
Western & Central Europe	850,000	30,000	0.3%	13,000
Global Total	33.4 million	2.7 million	0.8%	2.0 million

* Proportion of adults aged 15-49 who were living with HIV/AIDS

Table 1. Percentage HIV in the worldwide, end of 2008

Region	Adults & children living with HIV/AIDS	Adult prevalence*
Africa	22.7 million	5.4%
South-East Asia	3.8 million	0.3%
Oceania	59,000	0.3%
Latin America	2.0 million	0.6%
Caribbean	240,000	1.0%
Central Asia	1.5 million	0.7%
North America	1.4 million	0.4%
Europe	850,000	0.3%
Global Total	33.4 million	0.8%

* Proportion of adults aged 15-49 who were living with HIV/AIDS

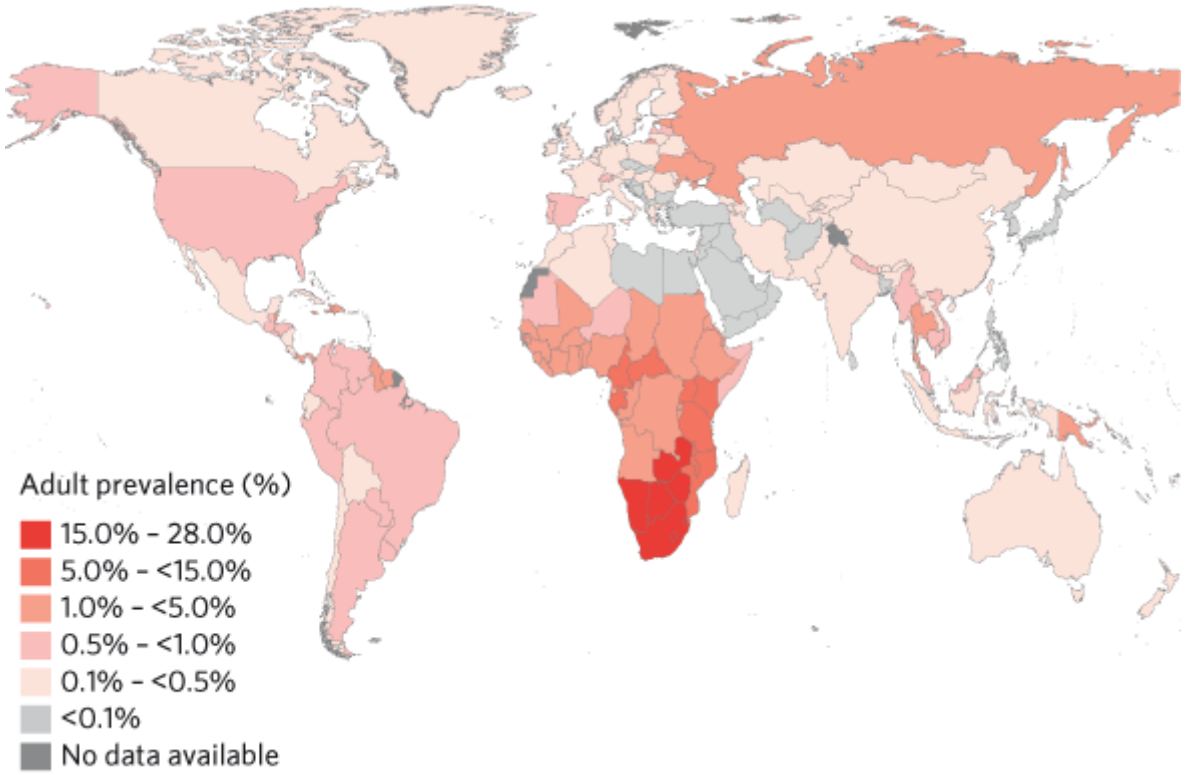

Figure 1. Percentage of HIV infection in 2008. (WHO/UNAIDS, 2008)

NRTIs, NNRTIs, PIs, and HAART

1. Nucleos(t)ide reverse transcriptase inhibitors (NRTIs)

NRTIs remain the most commonly prescribed ARVs and are always included in the initial treatment regimen. NRTIs are incorporated into the viral DNA, preventing reverse transcription and therefore inhibiting viral DNA synthesis and DNA polymerase. Viral replication is terminated and infection of new target cells is reduced (2).

Specific NRTIs are:

Zidovudine (AZT) is the oldest ARV and is still frequently used. Its major toxic effects include bone marrow suppression, gastrointestinal upset and headache. Zidovudine penetrates the central nervous system and has shown efficacy in settings such as prevention of intrapartum mother-to-child transmission (3)

Lamivudine (3TC) has activity against both HIV and hepatitis B virus (HBV), with few side effects. Used alone, HIV resistance to lamivudine emerges within weeks. HBV also acquires resistance to lamivudine at a greater frequency in HIV–HBV co-infected individuals than in HBV-mono-infected individuals(3).

Tenofovir *(TDF)* is a nucleotide NRTI that is well tolerated; nephrotoxicity (reduced creatinine clearance and/or Fanconi syndrome) has been reported and may occur in individuals with preexisting renal failure, and diabetes mellitus (3).

2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs act at the same step with NRTIs cycle, but do not require intracellular phosphorylation and do not inhibit human DNA polymerases. Nevirapine and efavirenz are the preferred NNRTIs in Australia (5).

NNRTI based regimens are commonly prescribed as initial therapy. These regimens generally have the advantage of established efficacy compared to protease inhibitor-based regimens.

The use of both nevirapine and efavirenz in the same regimen has been shown causes more adverse events than each drug separately (6).

Specific NNRTIs are:

Efavirenz *(EFV)* is highly potent and associated with high rates of central nervous system side effects, such as insomnia, irritability and psychosis. Efavirenz is teratogenic; therefore all women with childbearing potential should use effective contraception (5)

Nevirapine *(NVP)* is associated with rash and hepatotoxicity, and highly effective in prevention of intrapartum mother-to child transmission. Principles use of Efavirenz and nevirapine are equally effective, but differences in toxicity profile (6).

3. Protease inhibitors (PIs)

PIs mechanism is blocking the production of virus from infected cells. PI is referred to as a "boosted PI" regimen, and generally preferred to use without ritonavir boosting. Low-dose ritonavir will inhibit metabolism of the second PI leading to an increase in serum levels. PIs and ritonavir "boosted" PI regimens have improved pharmacokinetics, reduced pill burden, and a higher barrier to the development of ARV resistance(7). PI-based therapy is often used as an initial regimen and for therapy when multidrug resistant HIV has developed, however, there is no randomised controlled trial evidence for this use (7). The newer generation PIs (atazanavir, lopinavir) have the advantages of fewer side effects, and efficacy against HIV with multiple mutations (11).

Specific PIs are:

Lopinavir is well tolerated except for the common side effect of diarrhoea. It has a high barrier to viral resistance.

Atazanavir offers the advantage of once-daily dosing and is associated with less diarrhoea, dyslipidaemia and insulin resistance than other PIs. Comparison of an "un-boosted" atazanavir regimen with an efavirenz-based combination showed similar antiviral efficacy (8).

4. Highly Active Antiretroviral Therapy (HAART)

In 1996, highly active antiretroviral therapy (HAART) was introduced for people with HIV and AIDS. HAART is a combination of three or more drugs, such as protease inhibitors and other anti-retroviral medications. The treatment is highly effective in slowing the rate at which the HIV virus replicates itself, which may slow the spread of HIV in the body. The goal of HAART is to reduce viral load, to a level that can no longer be detected with blood tests.

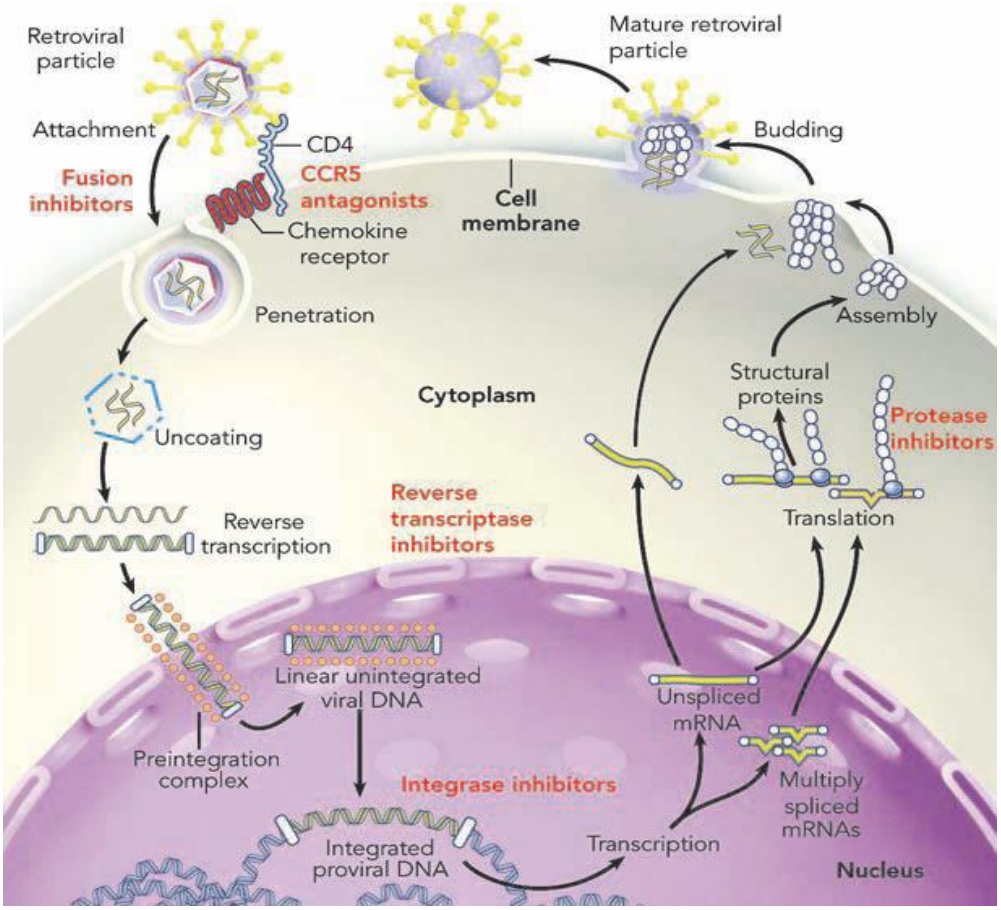

Figure 2. Antiretroviral Mechanism

Antiretrovirals Mechanism

ARVs work by suppressing HIV viral load and increasing CD4+ in the plasma. HIV RNA primarily infects CD4+ T lymphocytes, binds to the CD4 receptor and specific chemokine co-receptors. Virus and host cell membranes fuse and HIV RNA enters the target cell. The HIV RNA conducted RNA transcription to DNA and integrate with DNA host cells. Multiple copies of HIV RNA are made from the nucleus. Viral proteins are processed by the protease enzyme and packaged at the cell surface.

Combination vs Non-Combination

A protease inhibitor plus two nucleosides. Many studies has compared two nucleosides plus a protease inhibitor with a double-nucleoside combination and showed that three drugs given together result in a larger and longer-lasting reduction in viral load when compared with double-nucleoside combinations or with protease inhibitors used as single agents. Indinavir + AZT + 3TC is stronger and lasts longer than AZT + 3TC. Indinavir + AZT + ddI is stronger than AZT + ddI. Saquinavir + AZT + ddC is stronger than AZT + ddC.

A non-nucleoside and two nucleosides. The best results with the non-nucleoside nevirapine were in a study combining it with two nucleosides: AZT and ddI. As with protease inhibitors, the three-drug combination is stronger than the double-nucleoside combination. When combined with only one nucleoside, nevirapine did not work as well.

Nucleoside-nucleoside combinations From Cochrane reviewed on 2004, the most recommended regimens of NRTIs combination contain at least two NRTIs combined with an ARV from another class. Current preferred combinations of NRTIs are based on efficacy and toxicity, include zidovudine (AZT), didanosin (ddI), abacavir or tenofovir plus lamivudine (3TC), or emtricitabine plus tenofovir(4). Many Randomized Controlled Trial Study conducted in USA, Canada, and Australia showed that adding 3TC to AZT, to AZT + ddI, or to AZT + ddC would decrease virus in the blood and increase CD4 counts. It is likely that double-nucleoside combinations will be a part of anti-HIV therapy for a long time.

Why combinations therapy work well together?

Combinations therapy with two or more HAART with different modes of action **may overcome or delay virus resistance** compared to single agents. The most common drug combination consists of two NRTIs combined with either an NNRTI or a "boosted" protease inhibitor. An example of a common antiretroviral combination is the two NRTIs zidovudine and lamivudine, combined with the NNRTI efavirenz

How effective is HAART compared to the original HIV medication?

The nucleosides and non-nucleosides both have the same "target" to inhibit the action of the HIV RNA transcription by taking over the infected cell from nucleus and prevent multiple copies of HIV RNA. Nucleosides and non-nucleosides inhibit the action of the same HIV enzyme, reverse transcriptase, but it in a different way.

Protease inhibitors inhibit the action of another HIV protease enzyme. Enzyme protease works by cutting long chains of HIV proteins and enzymes into smaller pieces and preventing HIV to replicate new copies. The result of HIV new copies will then does not have ability to infect new cells.

Reverse transcriptase inhibitors (nucleosides and non-nucleosides) and protease inhibitor work at different steps in the process of HIV replication and that is why both are an effective combinations therapy of HAART, compared to single agents.

Table 2. Different Types of HAART Regimens

Combination	Mode of action	Advantages	Side effects
NNRTI-based • 2 NRTIs + NVP • 2 NRTIs + EFV	suppress HIV replication and reaches HIV in spinal cord and brain; works best in cells actively producing new HIV	• Low pill burden • Simple dosing schedule • Fewer metabolic complications than PI-based regimens • Preserves PI options for future regimen	Anemia (low number of red blood cells), granulocytopenia (low number of white blood cells), muscle weakness
PI-based • 2 NRTIs + LPV/r • 2 NRTIs + NFV	inhibit the action of another HIV protease enzyme to prevent virus becoming infectious	•High genetic barrier to resistance	Mostly mild side effects; nausea, diarrhea

Currently Prescribed Antiretrovirals

Current recommendations for initial therapy for HIV infection include the use of dual NRTI (AZT/3TC, TDF/FTC, ABC/3TC) with either an NNRTI (efavirenz or nevirapine) or a boosted PI (lopinavir/ritonavir). The selection of a suitable HAART regimen should account for factors such as pill burden, adverse effects, pregnancy potential, co-infection with hepatitis B or C, efficacy, and comorbidities such as renal disease or metabolic syndrome.

The rapid change in agents makes Australia does not publish its own guidelines. The US DHHS guidelines provide information and guidance on Australian specific scenarios.

Conclusion

The combinations of HAART using 2 NRTIs plus NNRTIs or PIs (zidovudine, abacavir or tenofovir plus lamivudine, or emtricitabine plus tenofovir) are more likely to become preferred treatment of HIV infection internationally and in Australia, especially for standard treatment-naive patient. The evidence demonstrate that these combinations are more effective to reduce viral load.

However, some antiretroviral should not be combined due to overlapping toxicities and potential viral antagonism. Furthermore, the challenges in the future will be in the management of HIV infection: these include reduction of side effects and drug resistance, and increased options for treatment-experienced patients.

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